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Evaluation of traumatic brain injury: Brain potentials in diagnosis, function, and prognosis

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ABSTRACT

The focus of this review is an analysis of the use of event-related brain potential (ERP) abnormalities as indices of functional pathophysiology in survivors of traumatic brain injury (TBI). TBI may be the most prevalent but least understood neurological disorder in both civilian and military populations. In the military, thousands of new brain injuries occur yearly; this lends considerable urgency to the use of highly sensitive ERP tools to illuminate brain changes and to address remediation issues. We review the processes thought to be indexed by the cognitive components of the ERP and outline the rationale for applying ERPs to evaluate deficits after TBI. Studies in which ERPs were used to clarify the nature of cognitive complaints of TBI survivors are reviewed, emphasizing impairment in attention, information processing, and cognitive control. Also highlighted is research on the application of ERPs to predict emergence from coma and eventual outcome. We describe primary blast injury, the leading cause of TBI for active duty military personnel in present day warfare. The review concludes with a description of an ongoing investigation of mild TBI, aimed at using indices of brain structure and function to predict the course of posttraumatic stress disorder. An additional goal of this ongoing investigation is to characterize the structural and functional sequelae of blast injury.

1. Introduction

A traumatic brain injury (TBI) occurs every 23 s in the United States (Brain Injury Association of America, 2007). In addition to hundreds of thousands of service members who have sustained TBI in recent years, the Centers for Disease Control and Prevention estimates that 1.7 million people in the United States sustain a TBI annually (Faul et al., 2010). Approximately 20% of these injuries are attributed to motor vehicle accidents (Faul et al., 2010), whereas the European Brain Injury Consortium estimated that more than half of all brain injuries in Europe resulted from "road traffic accidents" (Murray et al., 1999, p. 225). Other common causes of TBI include falls (35% of injuries in the United States) and striking/being struck by an object, including sports-related concussions (16% in the general population, 25% in those under the age of 14) (Faul et al., 2010).

Deficits after TBI vary in type and magnitude due to the strength of the injuring force and the locus and severity of the brain injury. The Department of Veterans Affairs/Department of Defense criteria for classifying a TBI as mild, moderate, or severe are based on the presence and duration of loss or alteration of consciousness and amnesia for the events surrounding the incident (see Table 1). In addition, score an the Glasgow Coma Scale (a behavioral assessment tool; Teasdale and Jennett, 1974) and neuroimaging results are considered (Management of Concussion/mTBI Working Group, 2009). Mild TBI (or "concussion") is the most common form of head injury; approximately 80 to 90% of head injuries are classified as mild (Cassidy et al., 2004; LaChapelle et al., 2008). Bazarian et al. (2005) estimated the annual incidence of mild TBI in civilian populations to be as high as one per 200 in the United States. There is abundant evidence that concussion alters brain potential indices of information processing; this research will be covered elsewhere in this publication (Broglio et al., 2011). The primary emphasis of the present review is on moderate to severe TBI.

There have been numerous scientific reports, some going back 50 years, linking TBI to cognitive impairment. Cognitive deficits following TBI include aspects of attention (Gentilini et al., 1989; Gronwall, 1976; Lezak et al., 2004; Mathias and Wheaton, 2007; Mirsky et al., 1991; Oddy et al., 1985; Reitan and Wolfson, 2000; Rosvold et al., 1956; Willmott et al., 2009) coupled with alterations in memory (Gronwall and Wrightson, 1981; Mathias and Wheaton, 2007; Oddy et al., 1985; Reitan and Wolfson, 2000; Ruff et al., 1989), problem solving (Cicerone and Wood, 1987; Dawson et al., 2004; Jarvie, 1960; Krpan et al., 2007; Levin et al., 1990; Temkin et al., 1995; Wayland and Taplin, 1985), language skills (Coelho et al., 1991, 1995, 2002; Davis and Coelho, 2004; Ellis and Peach, 2009; Hagen, 1984; Heilman et al., 1971; Holland, 1982; Stout et al., 2000; Wiig et al.,

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Table 1
Classification of TBI severity.[a]

Criteria	Severity		
	Mild	Moderate	Severe
Loss of consciousness (LOC)	0–30 min	>30 min but <24 h	>24 h
Alteration of consciousness/mental state	Brief, <24 h	>24 h	>24 h
Post-traumatic amnesia (PTA)	0–1 day	>1 and <7 days	>7 days
Glasgow Coma Scale (best score in the first 24 h)	13–15	9–12	<9
Structural neuroimaging	Normal	Normal or abnormal	Normal or abnormal

[a] Management of Concussion/mTBI Working Group, 2009.

1988; Yang et al., 2010), and cognitive control of behavior (Aubry et al., 2002; Collins et al., 1999; Ellemberg et al., 2007; Levin et al., 1987; Stuss et al., 1989). Information processing is slowed, often permanently, following the injury (Brouwer et al., 1989, 2002; Dikmen et al. 1986, 1995; Gentilini et al., 1989; Gronwall, 1989, Gronwall and Wrightson, 1981; Mathias and Wheaton, 2007; Ponsford and Kinsella, 1992; Reitan and Wolfson, 2000; Stuss et al., 1986, 1989; Willmott et al., 2009). Some cognitive deficits may be difficult or impossible to detect using standard neuroimaging methods. However, evoked potentials (EPs) and event-related brain potentials (ERPs) show promise in elucidating even subtle changes in sensory and cognitive processing.

2. Rationale for the use of ERPs to study cognitive sequelae of TBI

ERPs are one of the most informative and dynamic methods of monitoring the flow of information in the brain. The voltage deflections comprising the EP and ERP reflect the reception and evaluation of sensory information, as well as higher-level processing that involves selective attention, memory updating, semantic comprehension, and other types of cognitive activity. ERPs are linked in time with a physical event or mental activity. The ERP methodology is applicable to patients who are unable to respond orally or motorically, and thus provides a means to evaluate patients not suitable for conventional neuropsychological assessment.

An ERP component is defined by its positive or negative polarity,[1] amplitude, latency, scalp distribution, and relation to experimental variables. Components of the ERP are elicited in different paradigms and provide distinct types of information. Their sequence and latencies track the time course of processing activity in milliseconds (e.g., Duncan-Johnson, 1981; Duncan-Johnson and Donchin, 1982; McCarthy and Donchin, 1981; Näätänen et al., 1978; Sams et al., 1985). Their amplitudes indicate the extent of allocation of neural resources to specific cognitive processes required to analyze, categorize, and recognize stimuli (Donchin, 1981; Duncan-Johnson and Donchin, 1977, 1982; Näätänen, 1990; Näätänen and Picton, 1986; Pritchard et al., 1991; Ritter et al., 1979; Wickens et al., 1984). ERPs provide a non-invasive method of studying, with exceptional temporal resolution, information processing in the human brain.

3. Long latency ERP components used in TBI research

ERPs have been applied to TBI research to help elucidate and characterize deficits following brain injury. The cognitive ERP components applied most frequently to evaluate the effects of TBI include N100, mismatch negativity (MMN), N2b,[2] P3a,[3] P300,[4] error-related negativity (ERN), and post-error positivity (Pe). N100 reflects sensory processing of auditory stimuli (Davis and Zerlin, 1966; Näätänen and Picton, 1987), but is also sensitive to level of attention (Näätänen and Picton, 1987). Because the N100 component is primarily a sensory component, it is affected mainly by the physical characteristics of the eliciting auditory stimuli. The MMN is elicited by any discriminable change in a sequence of stimuli (Näätänen et al., 1978). This component is thought to reflect an automatic process that detects a difference between an incoming stimulus and the sensory memory trace of preceding stimuli. The MMN does not require conscious detection of a deviant stimulus.

N2b, P3a, and P300 are commonly elicited in the oddball paradigm, in which a random sequence of stimuli is presented. The stimuli can be classified into one of two or three categories, and the task is to classify the stimuli, either by counting or by pressing a button, to members of one category (the "target"). If members of the target category occur infrequently ("oddballs"), they will elicit N2b and P300. It is well established that the lower the probability of an attended stimulus, the larger the amplitude of P300 (Duncan-Johnson and Donchin, 1977). The N2b, P300, and P3a reflect aspects of information processing involved in stimulus discrimination, evaluation, and categorization (Clark et al., 1992; Courchesne et al., 1975; Duncan et al., 2003, 2009; Duncan-Johnson and Donchin, 1977, 1982; Näätänen and Picton, 1986; Ritter et al., 1982; Squires et al., 1975; Sutton and Ruchkin, 1984).

N2b is a component of negative polarity that is thought to reflect stimulus orienting (Czigler et al., 1996; Näätänen and Picton, 1986; Renault et al., 1982), recognition of stimulus relevance (Clark et al., 1992; Ritter et al., 1982; Spikman et al. 2004), and the conscious detection of deviance (Broglio et al., 2009; Duncan et al., 2005; Näätänen and Alho, 2004; Näätänen and Picton, 1986). It occurs approximately 200 ms after stimulus onset and is maximal over fronto-central brain regions (Spikman et al., 2004).

P300 is a positive-going component following N2b that is elicited by rare, attended stimuli (Duncan-Johnson and Donchin, 1977, 1982; Duncan et al., 2009; Johnson and Donchin, 1980; Johnson, 1989b; Kutas et al., 1977; Naito et al., 2005; Ruchkin et al., 1975; Sutton et al., 1965; Sutton and Ruchkin, 1984). It is typically elicited 300 ms or more after stimulus onset and is of maximal amplitude at centro-parietal electrode sites.

An additional component, P3a, can be elicited in the three-stimulus oddball task. This component reflects the identification and categorization of an unexpected, rare novel or deviant stimulus that does not require a response (the "no-go" stimulus; Courchesne et al., 1975; Snyder and Hillyard, 1976; Solbakk et al., 2002; Squires et al., 1975). In contrast to P300, which requires active attention to the eliciting stimuli, P3a can be elicited by attended or unattended sequences of stimuli. It is thought to be the neural correlate of the orienting response (Courchesne et al., 1975, Knight, 1984; Kok, 2001; Polich, 2007; Riggins and Polich, 2002; Rushby et al., 2005, Squires et al., 1975) and occurs somewhat earlier than P300, with a peak latency of 250–300 ms. It also has a more fronto-central distribution than P300 (Duncan et al., 2009; McDonald et al., 2010).

The error-related negativity (ERN) and post-error positivity (Pe) components have been used to evaluate deficits in cognitive control consequent to TBI. These ERP components are elicited by stimuli that provide feedback on task performance. The ERN is a negative response-locked ERP component elicited by incorrect responses. It

[1] Voltage difference between the recording and reference electrodes.
[2] The terms *N2b* and *N200* are used interchangeably in this review.
[3] The terms *P3a* and *novelty P3* are used interchangeably in this review.
[4] The terms *P300* and *P3b* are used interchangeably in this review.

peaks at approximately 100 ms and exhibits maximum amplitude over the midline fronto-central electrode sites (Falkenstein et al., 1991; Gehring et al., 1993). The ERN is thought to reflect the activity of a performance- and action-monitoring system when there is a mismatch between intended and produced responses or when competing response options are activated simultaneously (Falkenstein et al., 1991; Gehring et al., 1993; Holroyd and Coles, 2002; Yeung et al., 2004).

Following the ERN, the Pe is a positive response-locked ERP component elicited 100–400 ms after an incorrect response (Falkenstein et al., 1991; Overbeek et al., 2005). This component, with a midline centro-parietal scalp distribution, is thought to be associated with signaling for post-error adjustments in behavior and the conscious recognition of errors (Nieuwenhuis et al., 2001).

4. ERPs as indices of impaired attention and information processing after TBI[5]

4.1. Overview

The majority of ERP studies on N2b, P3a, and P300 have shown that in comparison to healthy controls, TBI survivors have ERPs of smaller amplitude (Campbell et al., 1990; Campbell and de Lugt, 1995; Clark et al., 1992; Deacon and Campbell, 1991; Deacon-Elliott and Campbell, 1987; Duncan et al., 2009; Rugg et al., 1988; Solbakk et al., 2002; Wirsén et al., 1992), longer latency (Duncan et al., 2003; Keren et al., 1998; Lew et al., 2007a; Olbrich et al., 1986; Reza et al., 2007; Sangal and Sangal, 1996; Spikman et al., 2004), or both (Doi et al., 2007; Duncan et al., 2005; Lew et al., 2004, 2005b, 2007c, 2009; Naito et al., 2005; Segalowitz et al., 1997). However, the findings are not consistent, and a number of variables have been shown to influence amplitude and latency deviations in TBI survivors (Campbell et al., 1990; Campbell and de Lugt, 1995; Deacon and Campbell, 1991; Deacon-Elliott and Campbell, 1987; Duncan et al., 2005; Elting et al., 2008). In Section 4.4, we review injury-related factors that have been shown to affect ERPs in TBI survivors. First, however, to provide needed context, we discuss the ERP task variables and methods of data quantification that have been implicated in the inconsistent findings.

4.2. ERP task variables

4.2.1. Stimulus characteristics

4.2.1.1. Stimulus modality. Stimulus modality affects the amplitude and latency of cognitive ERP components (Duncan et al., 1994, 2003, 2005, 2009; Johnson, 1989a, 1989b; Polich, 2007). The majority of ERP studies of TBI have used auditory tasks (Elting et al., 2005, 2008; Lew et al., 2007a; Naito et al., 2005; Reza et al., 2006, 2007; Rousseff et al., 2006; Sarno et al., 2006; Segalowitz et al., 1997, 2001; Solbakk et al., 1999, 2002). Others have used visual tasks (Broglio et al., 2009; LaChapelle et al., 2008; Lew et al., 2005b; Roche et al., 2004), and a few have used tasks in both modalities (Bernstein, 2002; Doi et al., 2007; Duncan et al., 2003, 2005; Gaetz and Weinberg, 2000; Lew et al., 2004, 2007c, 2009).

Lew et al. (2004) compared ERPs in TBI subjects (mean = 9 months post-injury) and controls as a function of stimulus modality. They observed no significant intermodal group differences, although there was a nonsignificant trend toward a longer latency of visual than auditory P300 in TBI survivors. In a subsequent study of TBI subjects (mean = 16 months post-injury), Lew et al. (2009) again compared ERPs elicited by visual and auditory stimuli. However, in this study, visual P300 had a significantly longer latency than auditory P300 in TBI survivors. The same modality difference was observed in the controls, a finding consistent with previous research on healthy subjects (e.g., Duncan et al., 1994; Johnson, 1989a, 1989b). In both Lew et al. studies, however, it was found that in comparison to controls, survivors of severe TBI had smaller and later P300s elicited by both visual and auditory stimuli. In the 2009 study, the largest difference between groups was in visual P300 latency, although the amplitude of visual and auditory P300 was both smaller in the TBI group. Gaetz and Weinberg (2000) reported a similar finding in their study of survivors of mild TBI. The authors noted that the primary difference between the mTBI and the control groups was in the latency of visual P300; between-group differences in auditory P300 latency were smaller.

In two studies of survivors of moderate and severe TBI, Duncan et al. (2003, 2005) administered visual and auditory stimulus discrimination tasks. All TBI survivors were tested at least two years post-injury. Duncan et al. reported that in the visual tasks, only the amplitude of N2b was reduced in the TBI survivors. In contrast, ERPs elicited by auditory stimuli differed considerably between groups. N2b was smaller, and N2b and P300 were later in the TBI survivors than in the controls. Duncan et al. (2003, 2005) suggested that this pattern of results indicates that the brain system supporting the processing of auditory stimuli is more vulnerable to trauma than that supporting visual processing.

4.2.1.2. Stimulus complexity. Lew et al. (2007c) evaluated the effects of stimulus complexity on P300 in survivors of severe TBI and healthy controls. They presented four types of stimuli: simple and complex visual tasks (color discrimination and facial affect discrimination) and simple and complex auditory tasks (tone discrimination and word category discrimination). As compared to controls, the TBI group, at 15.5 months after injury, had significantly reduced P300 amplitudes on three of the four tasks (all except the complex auditory task) and longer P300 latencies on the two simple tasks. There was a trend toward a delayed P300 on the complex visual task. The complex auditory task, the most demanding of the four tasks based on reaction time, failed to elicit a distinct P300. The authors maintained that this was because the complex auditory task, which required semantic categorization, was qualitatively different from the other tasks. The failure of the complex auditory task to elicit robust P300s in either TBI survivors or healthy controls is puzzling: Kutas et al. (1977), using the same task with visual stimuli, observed P300s to targets with latencies in the range of 500 ms and more than 25 μV in amplitude. Thus, the failure of this task to distinguish the groups may be due to the reduced discriminability of the complex auditory stimuli. Additionally, increased trial-to-trial variability of P300 could have accounted for the poor waveform morphology and low amplitude observed in the complex auditory task.

Solbakk et al. (2005) used affective visual stimuli to elicit ERPs in three groups: (1) survivors of mild TBI, (2) patients with frontal brain lesions confirmed by computed tomography (CT) or magnetic resonance imaging (MRI), and (3) healthy controls. Subjects responded to pleasant, unpleasant, and neutral stimuli, rating their perception of the stimuli's valence while ERPs were recorded. In each of the groups, affective stimuli elicited a larger P300 than neutral stimuli. However, the mild TBI group had smaller P300 amplitude in comparison to the other groups, regardless of picture valence. In contrast, although there were no group differences in the 300–500 ms latency range of ERPs at frontal, central, or parietal electrode sites, the frontal injury group had significantly larger P300s at occipital sites. This was evident for all valences of pictures. The authors suggested that this anomalous result might indicate a dysfunction of the "prefrontal modulation of activity in sensory-perceptual brain areas" (p. 220).

Doi et al. (2007) also used affective stimuli to assess survivors of TBI approximately two years after the injury. Visual stimuli were

[5] In this paper, we emphasize work published since Duncan et al.'s (2005) review, in the context of previous relevant studies.

presented of smiling (pleasant) and crying (unpleasant) babies, as well as neutral baby faces. The TBI group showed no P300 differences among the stimulus categories. In contrast, the controls had a shorter latency and larger amplitude P300 to the unpleasant than to the pleasant stimuli.

4.2.2. Task demands

Variations in the task used to elicit ERPs may also affect the results of studies of TBI survivors (Bernstein, 2002; Doi et al., 2007; Duncan et al., 2003, 2005; Lew et al., 2007c; Reza et al., 2006; Sarno et al., 2006; Segalowitz et al., 2001). Task variations include presenting an oddball paradigm in which auditory stimuli vary in duration (Bernstein, 2002; Segalowitz et al., 2001), using a motor response (button press) versus keeping a silent count of target stimuli (Reza et al., 2006), or counting silently versus passive listening (Sarno et al., 2006). Other manipulations involve varying task demands among discrimination tasks (simple, go/no-go, and choice response; Duncan et al., 2003) or using a challenging task (such as the Continuous Performance Test; Duncan et al., 2005).

Fig. 1 presents grand-average ERPs from the Duncan et al. (2003, 2005) studies. As described in Section 4.2.1.1, two-stimulus discrimination tasks yielded delays in auditory N2b and P300 (and a reduction in N2b amplitude; Fig. 1A) and group differences in response speed, but not in accuracy. In contrast, a more demanding task (Fig. 1B) produced reductions in P300 amplitude and fewer correct responses, but no differences in the latency of responses or ERPs. A possible explanation for the discrepant latency results in the two auditory paradigms may relate to the different instructional sets: In the discrimination task, response speed was emphasized; whereas in the CPT, the emphasis was on accuracy of performance.

Duncan et al. (2005) reported that P300 amplitude was reduced in moderate to severe TBI survivors only when the task was sufficiently demanding (i.e., a test of sustained attention [the Continuous Performance Test; Rosvold et al., 1956; Duncan and Mirsky, 2004] versus two-stimulus reaction time tasks). The authors emphasized the importance of adjusting task difficulty to the cognitive capacity of the subjects (Duncan et al., 2005). When the requirements of the task exceed the available processing resources, performance declines and P300 amplitude is reduced.

Sarno et al. (2006) administered passive (ignore) and active (counting) oddball tasks to survivors of severe TBI and healthy controls. In comparison to controls, N2b in TBI survivors was longer in latency in both active and passive conditions. Whereas they reported additional findings (e.g., differences in N2b elicited by standard tones), the results have to be viewed with some caution: Their equipment allowed recording from only one EEG channel and no electro-oculogram.

In a study of survivors of moderate to severe TBI, Reza et al. (2006) compared ERPs elicited in auditory oddball tasks requiring a silent count or a button press response. They observed that the counting task elicited P300s with longer latencies than those elicited in the button press task, although the difference was significant only at Cz. The authors suggested that the memory requirement of the counting task increased the cognitive load and thereby delayed P300.

4.3. Method of data quantification

Elting et al. (2005) used a two-tone oddball task to elicit P300s in survivors of moderate to severe TBI using both conventional (baseline-to-peak; Picton et al., 2000) and source analysis (Scherg and Picton, 1991) methods of quantifying P300 (see Fig. 2). With conventional analysis, P300 was smaller in amplitude and longer in latency in TBI survivors than in healthy controls. Whereas P3a was not evident using conventional analysis, using source analysis, it was evident in all controls and in 22 of 33 (67%) of the TBI survivors. Source analysis revealed no group differences in the latency of P3a or P3b (P300), but a reduction in the amplitude of P3a in the TBI group. This analysis technique has demonstrated that in healthy subjects, P3a and P300 overlap in time and therefore may only be quantifiable as separate components using source analysis or multivariate analysis techniques (e.g., principal components analysis; Dien et al., 2004; McDonald et al., 2010; Spencer et al., 2001).

4.4. TBI variables

4.4.1. Severity of injury

In recent studies using cognitive ERP components in severe TBI (Duncan et al., 2003; Lew et al., 2007c, Spikman et al., 2004), it was

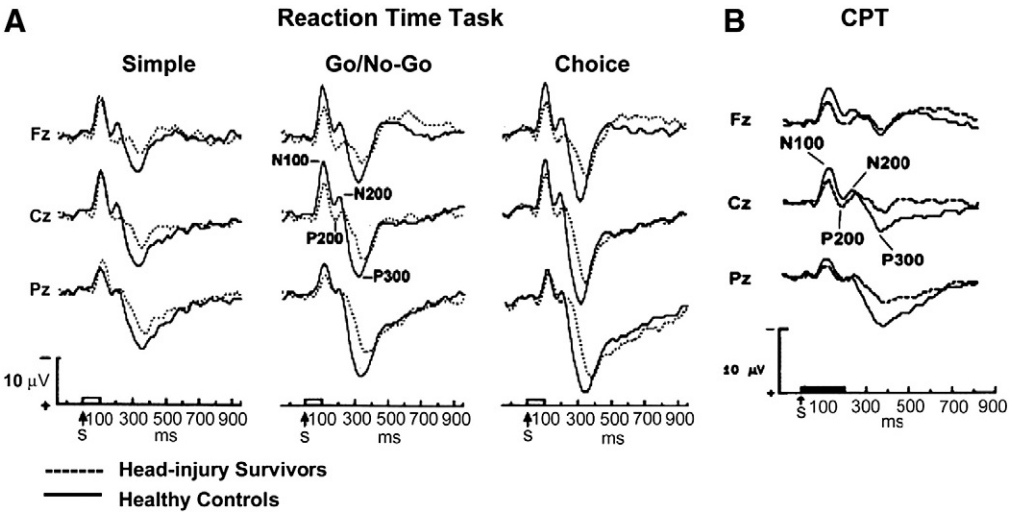

Fig. 1. (A) Grand-average ERPs elicited by rare stimuli ($p = .10$) in auditory simple, go/no-go, and choice two-stimulus reaction time tasks. The ERPs for head-injury survivors and healthy controls are superimposed at three midline electrode sites. As compared with controls, the survivors' N100 and N2b amplitudes were attenuated, and N2b and P300 latencies were delayed. The group differences in latency were reflected in significant differences in response speed but not accuracy. (B) Grand-average ERPs elicited by targets ($p = .25$) in a three-tone auditory Continuous Performance Test (CPT; Duncan and Mirsky, 2004; Mirsky et al. 2001). The ERPs for the head-injury survivors and healthy controls are superimposed at three midline electrode sites. The amplitudes of N100, N2b, and P300 were reduced in the survivors as compared to the controls. The smaller amplitudes in the survivors correspond to fewer detected targets on the CPT but no differences in response latency.
From Duncan et al., 2009, reprinted with permission.

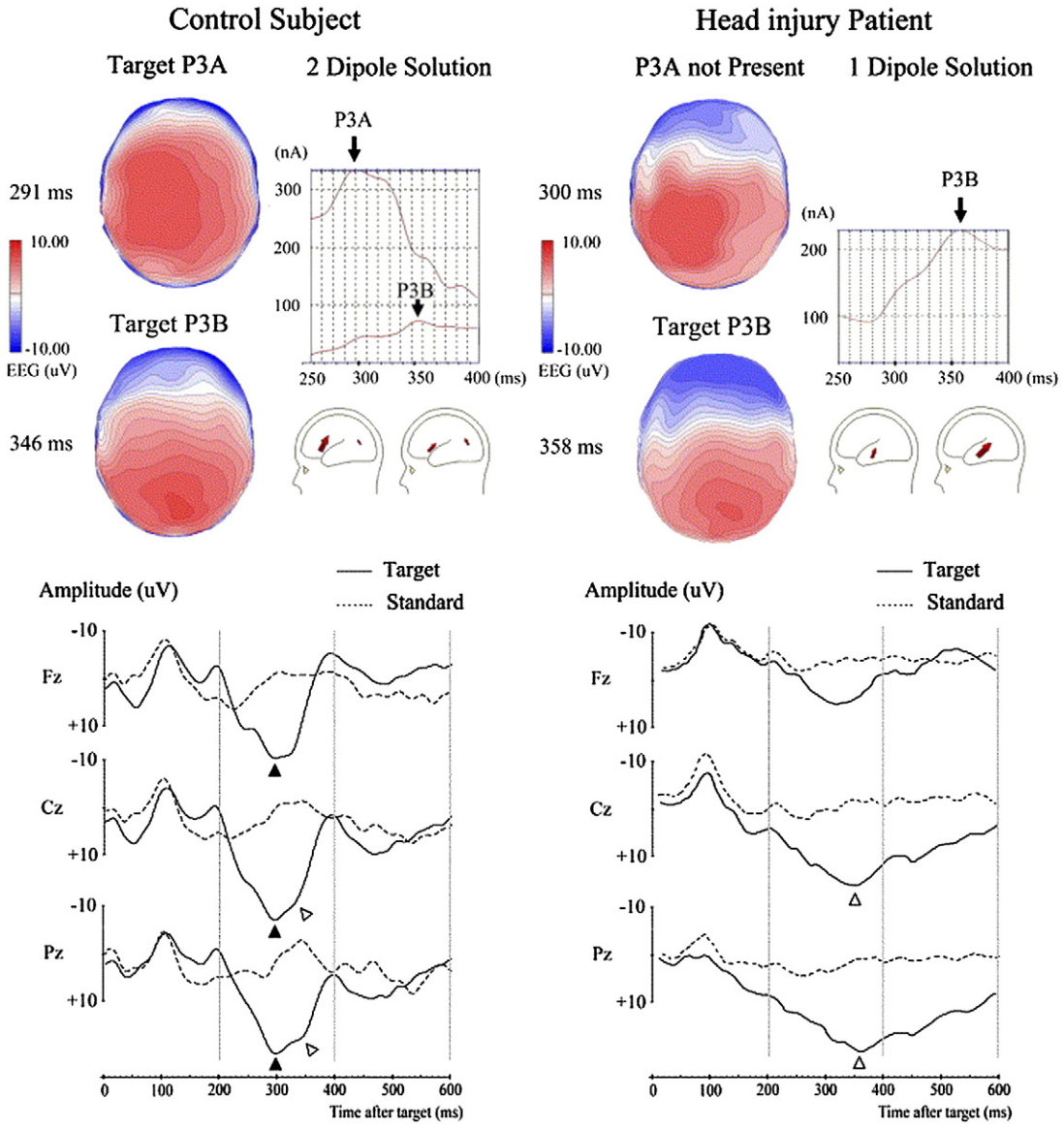

Fig. 2. ERP data recorded during an auditory oddball task. Results based on source analysis (upper half) and conventional P300 quantification (lower half) are displayed for a control subject (left) and a head-injury survivor (right). In the control subject, a 2-dipole solution identified both P3a and P3b (P300). Conventional analysis identified only P3b elicited by targets. Arrowheads on the ERP waveforms correspond with source analysis P3a (filled) and P3b (open). Whereas significant group differences in P3b latency and amplitude were identified using conventional analysis, source analysis identified only decreased P3a in the TBI group.
From Elting et al., 2005, reprinted with permission.

reported that amplitude was smaller and/or latency longer in TBI survivors as compared to healthy control subjects. In addition, it was noted that these relationships are affected by the time since injury, as well as the severity of injury.

Lew et al. (2007c; discussed in Section 4.2.1.2 above) studied survivors of severe TBI, 15.5 months after injury, using both simple and complex, auditory and visual stimuli. They reported that the duration of posttraumatic amnesia was highly correlated with reduced P300 amplitude, but only reached significance in the simple visual (color discrimination) and auditory (tone discrimination) tasks.

Spikman et al. (2004) also reported a correlation between posttraumatic amnesia and P300 in a group of survivors with moderate to severe TBI tested one year after injury. However, duration of posttraumatic amnesia was significantly correlated with the latency rather than the amplitude of auditory P300.

A significant association between the degree of injury severity and P300 latency in an auditory oddball task was reported by Rousseff et al. (2006). In this study, patients with concussion (mild TBI) were compared to those with verified contusion (moderate TBI) and to healthy controls. Subjects were tested 2 weeks to 28 months after injury. In the contusion group, most (16 of 20) of the patients had a delayed auditory P300; a small number had no P300. In contrast, the P300 amplitude and latency of the concussed group did not differ from those of the healthy controls.

As mentioned in Section 4.2.1.2, Solbakk et al. (2005) reported a different finding: i.e., reduced visual P300 in their concussed (mild TBI) group, but enhanced P300 at occipital sites in their frontally-contused group.

Others have also reported correlations between injury severity and ERP variables. Using two-stimulus auditory and visual discrimination tasks, Duncan et al. (2003) assessed survivors of moderate and severe head injury, who were at least two years post-injury. Using duration of unconsciousness as a measure of injury severity, highly significant correlations were found in auditory but not visual tasks between length of unconsciousness and N2b latency, P300 latency, and N2b amplitude.

Table 2
Summary of associations between injury severity and ERPs.

	Injury severity	Time since injury	Modality and task	Significant findings
Clark et al. (1992)	Moderate and severe	1–5 yrs.	Auditory three-stimulus oddball[a]	Negative correlation between duration of PTA[b] and parietal P300 latency to novel tones; authors noted that this finding may be spurious as the result is counter-intuitive
Bernstein (2002)	Mild	1 to 16.5 yrs. (M = 8 yrs.)	Auditory and visual oddball	No significant correlations between LOC[c] and P300 amplitude
Duncan et al. (2003)	Moderate and severe	>24 mos.	Auditory and visual oddball	Duration of LOC correlates highly with auditory but not visual ERPs: smaller, later N2b and later P300
Spikman et al. (2004)	Moderate and severe	12 mos.	Auditory oddball	Duration of PTA correlates with later auditory P300
Rousseff et al. (2006)	Mild and moderate	0.5 to 28 mos.	Auditory oddball	Moderates had delayed or missing P300; milds had normal P300 latency and amplitude
Doi et al. (2007)	Mild, moderate, and severe	16.8 to 34.6 mos. (M = 25.7)	Auditory and visual oddball	No correlations between GCS[d] (used to distinguish mild, moderate, and severe), P300, or N2b
Lew et al. (2007c)	Severe	M = 15.5 mos.	Auditory and visual oddball	Duration of PTA correlates with smaller P300 amplitude on auditory and visual tasks with simple versus complex stimuli

[a] Unless noted otherwise, the "oddball" task refers to two stimulus categories.
[b] Post-traumatic amnesia.
[c] Loss of consciousness.
[d] Glasgow Coma Scale.

Some investigators have reported no significant association between severity of injury and P300 (Bernstein, 2002; Clark et al., 1992; Doi et al., 2007). Nevertheless, the typical finding is that the amplitude and/or latency of cognitive ERP components are correlated with indices of TBI severity. This association may not be apparent in studies of mild TBI, possibly due to the restricted range of injury severity. Table 2 summarizes the findings on injury severity and ERPs: The preponderance of the evidence suggests that injury severity is associated with reduced amplitude of auditory N2b and P300 and increased latency of auditory P300.

4.4.2. Locus of injury

Recent studies of TBI survivors have used neuroimaging techniques to identify the locus of injury as a variable in relation to the ERP data. Studies of survivors of moderate to severe TBI have shown that the type and location of brain injury vary considerably. Diffuse axonal injury is the most common form of TBI (Arfanakis et al., 2002; Bazarian et al., 2007; Capruso and Levin, 1992; Evans, 1992; Filley, 2005; Inglese et al., 2005; Levine et al., 2006), followed by focal injury or a combination of the two (Naito et al., 2005; Reza et al., 2006). Because of their vulnerable locations within the bony ridges of the skull, contusional injury affects orbitofrontal cortex and anterior temporal lobe structures selectively (Gurdjan and Gurdjan, 1976; Jennett and Teasdale, 1981). The particular vulnerability of the temporal lobe structures, and the possible relevance to auditory processing difficulty in TBI survivors, was discussed by Duncan et al. (2005). They noted that TBI could lead to injury to primary auditory cortex via collision with the sphenoid bone and/or the petrosal ridge of the temporal bone.

Some recent ERP studies have used CT or MRI scans to identify the loci of lesions (Elting et al., 2008; Solbakk et al., 2002, 2005 [described above in Section 4.2.1.2]). In an extension of their 2005 study (reviewed in Section 4.3), Elting et al. (2008) recorded auditory oddball P300s in a larger sample of TBI survivors. They also collected MRI and neuropsychological data. Using conventional and source analysis to quantify ERP components, they replicated their finding that P300 is delayed and reduced in the TBI group when measured with conventional methods. When the components were quantified using source analysis, however, the amplitude of P3a differed significantly between groups: In comparison to the control group, P3a was smaller in the TBI group, but did not differ between those TBI survivors with normal versus those with abnormal MRIs. With respect to those survivors with frontal and/or temporal lesions, Elting et al. reported that medial frontal damage was associated with *reduced* P3a amplitude and orbitofrontal damage with *increased* P3a amplitude.

Solbakk et al. (2002) had similar findings. They assessed 18 moderate to severe TBI survivors (as confirmed by CT or MRI) using an auditory three-stimulus paradigm. As compared to the healthy control group, the TBI group had smaller P300 amplitudes and longer P300 latencies to targets. TBI survivors also exhibited a trend toward later P3a to novel stimuli (burst of white noise). As in the Elting et al. (2008) study, Solbakk et al. (2002) found that P3a amplitude was reduced when frontal or fronto-temporal brain regions were injured. The findings of both groups suggest that P3a amplitude is affected by frontal or fronto-temporal lesions. Their results are in accord with previous studies by Knight and co-workers (e.g., Knight, 1984; Knight et al., 1995; Knight and Nakada, 1998) showing that frontal lobe integrity is necessary for generating a normal P3a component.

In contrast, Kaipio and co-workers (Kaipio et al., 1999, 2000) observed that patients with severe TBI had larger P3a amplitudes than matched controls. The authors interpreted the P3a difference as evidence of greater involuntary switching of attention to acoustic changes in the TBI survivors, reflecting their increased distractibility.

4.4.3. Time since injury

The amount of time between brain injury and ERP assessment varies widely across studies. In some investigations, TBI survivors were tested approximately nine months after injury (Lew et al., 2004); whereas in others, data collection occurred several years after injury (Solbakk et al., 1999). Time since injury can vary even within a study: Sarno et al. (2006) tested TBI survivors 25–763 days post-TBI and reported that time since injury was not correlated with ERPs elicited in either active or passive auditory oddball tasks.

Lew et al. (2007a) used an auditory oddball paradigm to evaluate clinically recovered survivors of moderate to severe TBI on two occasions. The TBI survivors had been injured no more than two years prior to evaluation. The test–retest interval ranged from two days to two months (median interval = 43 days). At the initial testing, P300 latency was delayed significantly in the brain-injured group, as compared to the healthy control group. Upon retesting, the control group's P300 had remained stable, while the TBI group's P300 amplitude and latency changed, but not systematically. Overall, on retest, the ERPs of the TBI survivors had begun to normalize; the significant delay in auditory P300 latency observed initially was absent at retest. Lew et al. suggested that the normalization in the TBI survivors could be due to recovery over time. However, they also noted that the survivors were considered clinically recovered at the time of the initial testing. If the Lew et al. (2007a) study were to be replicated, it would be crucial to delineate and document the clinical state of the TBI group on both occasions.

The findings of Sivák et al. (2008) differ from those of Lew et al. (2007a). Using a two-stimulus auditory oddball paradigm, Sivák et al. tested controls and survivors of mild TBI shortly after injury and again three to seven months later. No significant differences in N2b or P300, either between or within groups, were observed. The differences between this research and Lew et al. (2007a) may be related to the differences in injury severity in the two TBI samples.

4.5. ERP indices of cognitive control

The concept of cognitive control has emerged in recent years as an exemplar of what is referred to more generally as "executive function." Cognitive control comprises two related and interactive sets of processes: one that evaluates and signals the need for regulative control and/or the presence of response conflict, and one that supports regulation, i.e., activates corrective maneuvers (Botvinick et al., 1999, 2001; Larson et al., 2007a; MacDonald et al., 2000; Perlstein et al., 2006). A growing area of research has yielded ERP components that reflect these evaluative and regulative processes.

Survivors of severe TBI have been shown to exhibit impairment in cognitive control (e.g., Flashman and McAllister, 2002; McAvinue et al., 2005; O'Keeffe et al., 2004, 2007; Sherer et al., 1998). Larson, Perlstein, and colleagues have applied ERPs to investigations of these deficits in a series of related studies. In one of their early studies, performance monitoring, an evaluative control process, was examined in survivors of severe TBI and matched healthy subjects using a modified color-naming version of the Stroop task (Larson et al., 2007a). The Stroop task has been used frequently in cognitive control studies because its stimuli provide conflicting cues. In the standard Stroop test, the time required to name the ink color in which a word is printed is increased if the word spells a conflicting color name (for example, the word *blue* printed in red ink; Stroop, 1935; see also Duncan-Johnson and Kopell, 1981). Response-locked ERPs, displayed in Fig. 3, include an early negative component—the error-related negativity (ERN)—that was larger in amplitude on error trials than on correct trials in both groups. Whereas there was no main effect of group on ERN amplitude, there was a significant Group × Accuracy interaction. Namely, in comparison to the control group, ERN was smaller on error trials in the TBI group; however, it did not differ between groups on correct trials. The amplitude of the centro-parietal Pe did not distinguish the groups. These results indicate that the performance-evaluating system, as reflected by the ERN, is impaired in survivors of severe TBI.

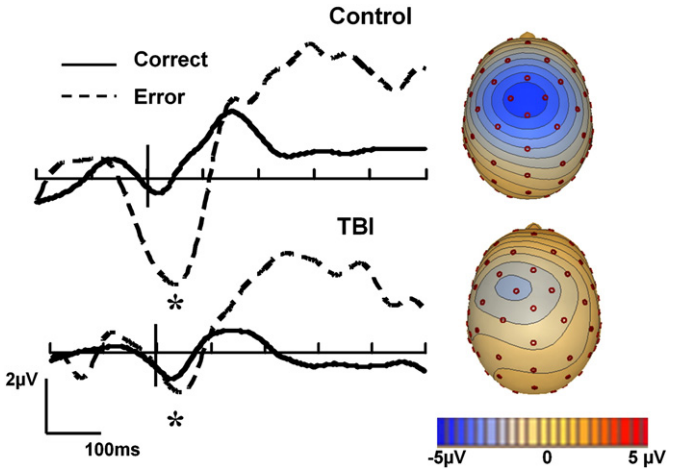

Fig. 3. Grand-mean ERPs depicting response-locked waveforms for correct (———) and error (- - - -) trials in the control and TBI groups. The fronto-medial ERN is indicated by an asterisk. At right is the top view of the spline-interpolated voltage distribution maps showing mean voltage at 22 ms for error trials in the control and TBI groups.
From Larson et al., 2007a, reprinted with permission.

Larson et al. (2009a) used the same color-naming version of the Stroop task to evaluate the effects of negative affect on ERN and Pe indices of performance monitoring. They predicted that negative affect would have a detrimental effect on performance monitoring in TBI survivors. Specifically, when compared to controls, TBI survivors with high levels of negative affect would show disproportionately attenuated ERN and Pe amplitudes. The results indicated that TBI survivors showed reduced ERN that decreased proportionately with increased negative affect. In contrast, in controls, ERN amplitude did not differ as a function of negative affect. The Pe component did not differ between groups or vary in relation to negative affect.

Larson et al. (2009b) also used the color-naming Stroop task to evaluate conflict adaptation effects. The authors predicted that these effects would be exhibited by a decreased Stroop effect (incongruent[6] minus congruent[7] trial difference) that was more pronounced when high conflict (incongruent) trials preceded the current trial, rather than low conflict (congruent) trials. They also expected the effects to be evidenced by smaller N450 (West and Alain, 1999, 2000) and conflict slow potential (West, 2003) components during high conflict trials. Whereas there were no group or trial category differences in N450, the conflict slow potential at the centro-parietal sites distinguished incongruent from congruent trials. Moreover, consistent with previous findings, controls had smaller conflict slow potential for trials that were preceded by incongruent presentations. This decreased Stroop effect was not evident in TBI survivors, suggesting less sensitivity to conflict adaptation. The investigators interpreted their results to indicate that in TBI survivors, there is a loss of conflict resolution mechanisms, as seen in the context of a reaction time task. The conflict slow potential difference in controls was 0.6 μV, as compared to 0.38 μV for the TBI survivors (see Table 4 in Larson et al., 2009b); thus, the group difference in sensitivity is a modest one. Replication in another TBI group would be necessary to conclude that the conflict slow potential measure is a reliable assay of TBI effects.

In the population of brain injury survivors studied extensively by this group of investigators, Pe did not differentiate the TBI and control groups. Only one study (Larson and Perlstein, 2009) found an altered Pe in TBI patients: In this study, Pe amplitude was associated with "awareness of deficit," defined as the discrepancy between survivor and primary caregiver ratings on the Frontal Systems Behavioral Scale (Grace and Malloy, 2001). Less awareness of deficits was associated with smaller Pe amplitudes, suggesting that Pe reflects a control process that underlies awareness of deficits and performance errors. In addition, the authors stated that the processes underlying Pe and awareness of deficits appear to overlap with attention. If this were the case, it would be expected that Pe amplitude would be reduced in TBI. Reduction in P300 amplitude is a highly replicated finding in TBI (Duncan et al., 2005; LaChapelle et al., 2008; Lew et al., 2004; Segalowitz et al., 1997). Duncan et al. (2005; reviewed in Section 4.2.2) found that decrements in P300 amplitude were only present when tasks were sufficiently demanding. Thus, it may be that the tasks used to elicit Pe were not difficult enough to reveal Pe differences.

In a study assessing reward context utilization in survivors of severe TBI, Larson et al. (2007b) used a guessing task (Holroyd et al., 2003; Ruchsow et al., 2002; van Meel et al., 2005) to assess subjects' response to feedback. In this task, subjects have several response options, but are told that only one is associated with reward. Following the response, feedback is presented to the subject indicating whether the response was correct (reward obtained) or incorrect (no reward). Subjects were not told that the reward feedback was pseudo-random and based on one of two conditions (high- and low-reward probability). In the high-probability condition,

[6] An example of an incongruent trial is the word *red* written in blue ink.
[7] An example of a congruent trial is the word *red* written in red ink.

subjects received positive feedback on 75% of the trials; in the low-probability condition, subjects received positive feedback on only 25% of trials. The manipulation of feedback was intended to establish an expectation of likely or unlikely reward. Feedback-locked ERPs were characterized by N100 and a feedback-related negativity (FRN).[8] The FRN, thought to occur when an error processing system detects that events are worse than expected, was elicited at a mean latency of approximately 250 ms with a medio-frontal scalp distribution. Whereas the main effects of group and feedback condition on FRN were nonsignificant, there was a significant Group × Feedback interaction, such that FRN was larger following non-reward than reward feedback in controls but not in TBI survivors. In fact, in TBI survivors, FRN amplitude was greatest when reward feedback was given in the low-probability condition. Larson et al. (2007b) interpreted the lack of difference between reward and non-reward in the high probability condition and the larger amplitude to reward in the low-probability condition as evidence of overall deficiencies in reward-context sensitivity following severe TBI.

4.6. Comment

Task and patient differences may help to account for the discrepancies in findings (and interpretations) among studies. Of note is the heterogeneity of the TBI samples in terms of severity, time since injury, and locus of injury (Lezak et al., 2004).The methodology used to elicit, record, quantify, and evaluate ERP data may also influence the results (Duncan et al., 2009; Picton et al., 2000). Some consensus about methods among laboratories may be necessary before the differences in findings can be resolved (Duncan et al., 2009). Nevertheless, the discrepancies emphasize the activity and vitality of this crucial area of research, as well as the need for further investigation and standardization of methods. High quality research must be supported, and reproducible findings must be achieved in order to best inform the diagnostic and remedial efforts that are urgently needed for TBI survivors.

Research from the Perlstein and Larson laboratories has demonstrated altered ERN, Pe, and FRN components of the ERP in survivors of severe TBI, suggesting impairment in performance monitoring, contingency sensitivity, and reward prediction (Larson et al., 2007a, 2007b, 2009a, 2009b; Larson and Perlstein, 2009). The finding of impaired sensitivity to reward context adds to the results of other studies indicating that, in comparison to healthy subjects, severe TBI leads to difficulties in monitoring one's own performance and in altering behavior in response to environmental cues, whether indicative of positive or negative consequences.

These highly salient findings are of fundamental importance in characterizing the cognitive deficits in TBI patients and in devising remediation methods. It would appear, however, that the Larson and Perlstein findings are based largely on a single group of approximately 20 TBI patients. It is therefore imperative to replicate these findings on other, larger groups with a variety of lesions. This would enable the correlation of lesion location, clinical symptoms, and ERP abnormalities. Such research would also contribute to our understanding of the sources in the brain of ERP components reflecting evaluative and regulative control.

5. ERPs in coma assessment

5.1. Introduction

Whereas any brain injury has the potential to cause cognitive and functional impairment, severe TBI can result in coma. Because coma may not be permanent, the question arises as to how to predict outcome and facilitate recovery. The Glasgow Coma Scale (Teasdale and Jennett, 1974) and neuroimaging methods, such as CT, MRI, and positron emission tomography (PET), have proven to be of limited value in the assessment of consciousness and the prediction of recovery from coma (Gawryluk et al., 2010; Lew et al., 2006; Wang et al., 2004). Newer neuroimaging techniques, including diffusion tensor imaging (DTI; Basser et al., 1994) and functional MRI (fMRI; Belliveau et al., 1991) may have the potential to provide sensitive information about the injury, but they are costly and require access to facilities with advanced imaging capabilities. Moreover, fMRI has a low signal-to-noise ratio and is therefore time-consuming, is sensitive to movement artifact, and has poor temporal resolution. ERPs may offer a more practical alternative to imaging and have demonstrated sensitivity to coma monitoring and outcome prediction (Fischer et al., 2004, 2008, 2010; Lew et al., 2003, 2006).

5.2. Mismatch negativity: positive predictive value

The MMN component of the ERP appears to have the greatest potential for predicting emergence from coma and eventual outcome (Daltrozzo et al., 2007; Fischer et al., 2004, 2008). It is ideally suited for assessing the comatose state, as it can be elicited regardless of the subject's level of wakefulness (Fischer et al., 2004, 2008; Näätänen and Winkler, 1999; Näätänen et al., 2007). In coma patients, the presence of MMN is associated with high rates of awakening, and is rarely elicited in those who do not recover (Fischer et al., 2004, 2008, 2010; Fischer and Luauté, 2005; Lew et al., 2006). Fischer et al. (2004) reported that no one in whom an MMN was elicited evolved into a permanent vegetative state one year after ERP assessment. In Fischer et al. (2010), ERPs were measured in TBI patients who had been diagnosed as being in a permanent vegetative or minimally conscious state and were in a coma for at least one year. This condition is associated with a low chance of awakening (Multi-Society Task Force on Persistent Vegetative State, 1994a, 1994b). Very few MMNs were elicited in their patients, a finding consistent with those of other studies, which also report that most patients will awaken from coma if MMN is elicited (Fischer et al., 2010).

For MMN, sensitivity[9] rates as high as 89.7% (Kane et al., 1996) and specificity[10] rates as high as 100% (Fischer and Luauté, 2005; Kane et al., 1996) have been demonstrated. Other studies have reported similar rates of sensitivity and specificity, making MMN a valuable prognostic tool (Fischer et al., 2004, 2008; Lew et al., 2006). Fischer et al. (2000) showed that when MMN was present, 30 of 33 (90.9%) subjects awoke from coma. Such high rates of specificity make MMN useful for tracking recovery and for developing a treatment plan for the comatose patient. Wijnen et al. (2007) found that subjects with larger and earlier MMNs at initial evaluation were more likely to have higher levels of consciousness at discharge (see Fig. 4) and better functional outcome two years after injury.

5.3. N100: positive and negative predictive value

In addition to MMN, the N100 component of the ERP can be elicited in comatose patients. In fact, in patients in whom MMN is present, N100 can almost always be elicited as well (Fischer et al., 2000, 2004, 2008; Luauté et al., 2005). The N100 component has thus been used to predict recovery from coma (Fischer et al. 2004; Lew et al., 2003, 2006; Luauté et al., 2005; Mazzini et al., 2001). Lew et al. (2003) found that both N100 and P300 predicted favorable clinical

[8] The ERN is elicited following an incorrect response, whereas an FRN is elicited to feedback after erroneous responses.

[9] Sensitivity is the ability to detect the maximum number of *true positives*. The formula for sensitivity is (*true positives*)/(*true positives* + *false negatives*). In the case of ERP and coma, it reflects the ability to predict which patients will awaken from coma.

[10] Specificity is the ability to detect the maximum number of *true negatives*, while minimizing *false negatives*. The formula for specificity is (*true negatives*)/(*true negatives* + *false positives*). In the case of ERP and coma, it reflects the ability to predict which patients will not awaken from coma.

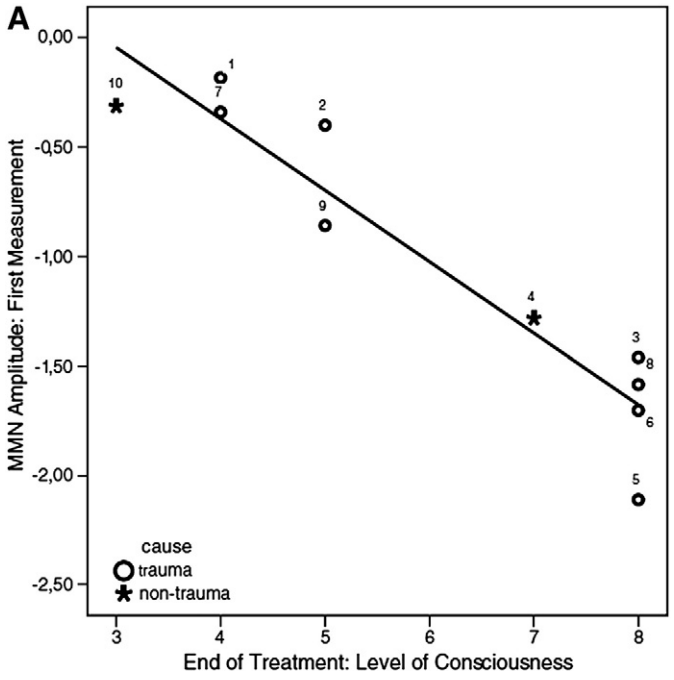

Fig. 4. The amplitude of MMN at the first evaluation plotted as a function of level of consciousness at the end of treatment. Larger numbers on the x-axis correspond to higher levels of consciousness, and larger amplitudes of MMN on the y-axis are more negative. Each number (1–10) corresponds to one patient.
Adapted from Wijnen et al., 2007, with permission.

outcome, providing additional evidence that the N100 component is associated with active information processing, as well as sensory processing. Furthermore, Fischer et al. (2008) reported that the predictive value of N100 and middle latency auditory EPs in TBI are superior to that of P300 or MMN. However, they noted that additional studies with larger samples are needed to support that conclusion.

Fischer et al. (2004) reported that N100 has value in predicting awakening. When N100 was present, 159 of 198 (80.3%) subjects awoke and only one progressed to a permanent vegetative state. No subject in whom both N100 and MMN were elicited was minimally conscious or in a vegetative state one year after assessment (Fischer et al., 2004). Regression analysis indicated that the best predictive model of awakening comprised the presence of N100, pupillary light reflex, middle latency auditory EPs (Na and Pa), patient's age, and etiology of injury. Similarly, Luauté et al. reported that the best prognostic variables were pupillary reflex and N100 in TBI and neurosurgery coma subjects. The estimated probability for a good functional outcome was 69 of 94 (73%) when pupillary reflex was present and increased to 47 of 55 (86%) when both pupillary reflex and N100 were present (Luauté et al., 2005). Using logistic multivariate regression analysis, they created a model using age, pupillary light reflex, and N100_MMN[11] that predicted functional outcome with high accuracy (Luauté et al., 2005).

In another study, Lew et al. (2003) observed that an absence of N100 and P300 had 66.7% specificity in the prediction of an unfavorable coma outcome (Glasgow Outcome Scale-Extended [GOSE] score of 1 to 4; Wilson et al., 1998). When N100 was present (categories A[12] and B[13]), the specificity in the prediction of the best outcome (GOSE score 7 or 8) from coma was 100% (Lew et al., 2003). Lew et al. (2006) reported that the N100 component had better negative[14] (as opposed to positive) predictive[15] value (89%) than short-latency somatosensory EPs (SEPs; 69%). When N100 was used in conjunction with SEPs, there was 100% sensitivity in predicting a poor outcome (Lew et al., 2006). Thus, the absence of both N100 and short-latency SEPs predicted that subjects would not awaken from coma. Nevertheless, in the study of Fischer et al. (2004), even when N100 was absent, 77 of 148 subjects (52%) awoke.

5.4. P300 And P3a: higher-level processing capacity

Recent studies have evaluated the P300 and P3a components in permanently vegetative or minimally conscious patients to assess cognitive capacity during these states (Laureys et al., 2004; Perrin et al., 2006; Schnakers et al., 2008) and to predict awakening from coma (Daltrozzo et al., 2007; Fischer et al., 2008, 2010; Lew et al., 2006). As described in Section 3, the P300 is elicited by task-relevant stimuli that are categorized as rare (Donchin, 1981; Duncan et al., 2009; Duncan-Johnson and Donchin, 1977); and previously, P300 had been considered unsuitable for prediction of coma outcome because it requires attention to stimuli. However, coma researchers are using meaningful words, such as “mommy,” as the target, and the results have shown promise in the prediction of awakening (Lew et al., 2003).

The P3a, which has an earlier latency than the P300, is elicited in response to novel, unexpected stimuli that are distinct from the target and standard stimuli (Elting et al., 2008; Polich, 2007; Solbakk et al., 2002). Studies evaluating coma patients have used the subject's own name as the novel stimulus to elicit a P3a (Fischer et al., 2008, 2010; Perrin et al., 2006). One study concluded that P3a might be a better measure of outcome than MMN in comatose subjects (Fischer et al., 2008). Using the subject's name as the novel stimulus in a three-stimulus task, Fischer et al. (2008) found that P3a and MMN were significantly correlated. There was also a highly significant correlation between P3a (but not MMN) and awakening (Fischer et al., 2008).

P3a was observed in 21 of their 50 patients. Fig. 5 displays ERPs elicited by the subject's name for three patients, two of whom (B and C) show P3a (Fischer et al., 2008). Also shown are scalp potential maps for two latencies identified as P3a and P300. The meta-analysis conducted by Daltrozzo et al. (2007) failed to demonstrate that P300 was a better predictor of recovery than the MMN. Whereas the likelihood of awakening from coma after TBI when P300 was elicited was greater than when MMN was elicited, the effect was nonsignificant ($p = .754$, Daltrozzo et al., 2007). Moreover, Fischer et al. (2010) found that P3a (albeit with prolonged latency) was elicited in five of nine non-anoxic[16] patients. They also tentatively identified P300 in two of the patients, which may have been indicative of higher levels of consciousness. Unfortunately, the Fischer et al. (2010) study did not report whether any of their patients ultimately emerged from coma.

P3a and P300 have been found repeatedly to be indicators of awakening from coma. Thus, their presence suggests that cognitive, as well as sensory, processing is, at least partially, intact in comatose patients (Fischer et al., 2008, 2010; Lew et al., 2006; Wang et al., 2004). Fischer et al. (2008) found a significant correlation between the proportion of subjects who awoke and the presence of the P3a. MMN was not significantly correlated with outcome, nor did it add to the predictive value of P3a. It is of interest that five of the seven subjects who awoke without having P3a were TBI survivors (Fischer

[11] N100_MMN is an ordinal variable defined as follows: (a) N100 absent, (b) N100 present, MMN absent, or (c) both N100 and MMN present.
[12] Category A in the Lew et al. (2003) study refers to the presence of both a normal N100 and normal P300 component.
[13] Category B in the Lew et al. (2003) study refers to the presence of an abnormal N100 component and the absence of a reproducible P300 component.
[14] Negative predictive value is the percentage of *true negatives*, compared to all subjects who tested *negative*. The formula for negative predictive value is (*true negatives*)/(*true negatives* + *false negatives*). In the case of ERP and coma, it reflects the ability to predict which patients will not awaken from coma.
[15] Positive predictive value is the percentage of *true positives*, compared to all subjects who tested *positive*. The formula for positive predictive value is (*true positives*)/(*true positives* + false positives). In the case of ERP and coma, it reflects the ability to predict which patients will awaken from coma.
[16] Non-anoxic subjects in the Fischer et al. study had the following etiologies: TBI ($n = 4$); stroke ($n = 4$); and viral encephalitis ($n = 1$).

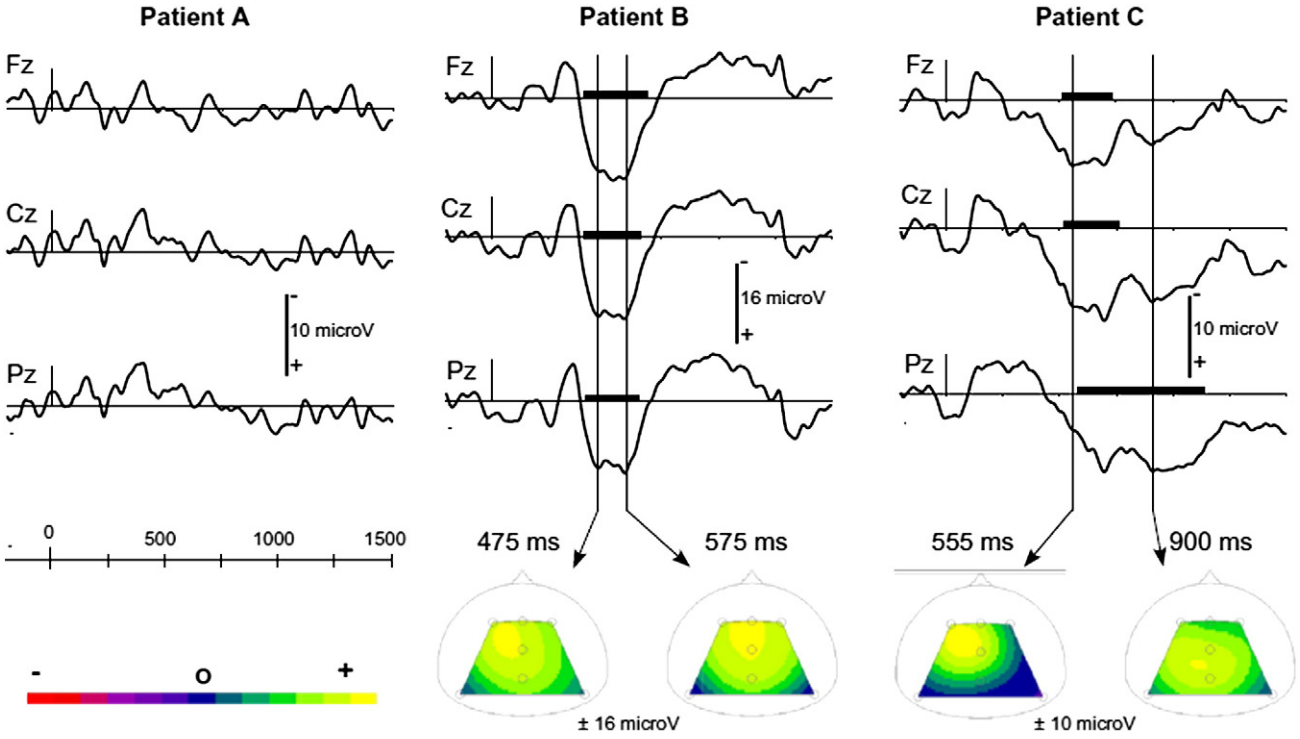

Fig. 5. ERPs elicited by rare ($p = .03$) auditory presentations of the patient's own name shown at three midline electrode sites. Data for three patients are displayed. Patient A showed no response to the novel stimuli. Patients B and C both showed a P3a, and a later positive peak with a parietal distribution (identified as P300) was observed in Patient C. These findings appear to be related to current clinical outcome. As of November 2010, Patient A remains in a vegetative state. Patients B and C both awoke, but with different outcomes. Patient B improved slowly and has permanent severe disability, whereas Patient C recovered consciousness within two weeks of coma onset with only moderate disability (C. Fischer, personal communication, November 5, 2010). Scalp potential maps using a spherical surface spline interpolation algorithm are presented in the lower part of the figure. From Fischer et al., 2008, reprinted with permission.

et al., 2008). Similarly, Lew et al. (2003) demonstrated that subjects with both normal N100 and P300 components had better outcomes one, three, and six months after onset of coma (Lew et al., 2003).

5.5. Comment

This overview of research on the use of ERPs to predict recovery from coma, and subsequent functional states, indicates the heuristic and practical value of these measures. ERPs as predictors of emergence from coma can differ based on etiology. Except when noted otherwise, all data presented in Section 5 are based solely on TBI-induced coma. The consensus would appear to be that the use of N100, MMN, P300, and perhaps P3a in various combinations, has great prognostic value for both awakening and cognitive recovery. The particular choice of components differs among investigators, but the use of ERPs in assessing coma would appear to be an essential, if not mandatory, aspect of medical practice.

6. Blast TBI

6.1. Overview

The research described above was based on brain trauma resulting from impact injuries. In recent years, another cause of TBI has been identified, explosive blast. In fact, primary blast-related TBI (primary blast TBI) has become the signature wound of the Iraq and Afghanistan wars (DePalma et al., 2005).[17] Blast has been implicated in the high incidence of later posttraumatic stress disorder (PTSD), depression, and other psychiatric disorders among returning service members (Elder and Christian, 2009; Hoge et al., 2008; Trudeau et al., 1998). Primary blast TBI is also becoming increasingly prevalent in civilian populations, as insurgents and terrorists gain access to military-grade high explosives. It has yet to be determined to what extent the existing scientific literature on TBI, based on studies of patients sustaining low-velocity trauma (e.g., sports injuries, motor vehicle accidents, and falls), is relevant to primary blast TBI (Anderson, 2008; Falik, 2009; Trudeau et al., 1998). Even the few studies on TBI survivors injured by low-order explosives, such as propellants (black powder) and pyrotechnics (fireworks), appear to be of limited applicability (Pennardt and Lavonas, 2010). This seems to be related to the differing physical effects of blasts produced by low- versus high-order explosives.

6.2. Taxonomy

As shown in Fig. 6 (Taber et al., 2006; top curve), the supersonic shock wave uniquely produced by high explosives passes through the head in less than 1 ms, causing an almost instantaneous overpressure, followed by a longer wave of underpressure, and a second wave of overpressure (Elder and Christian, 2009). Animal studies have shown that in addition to physical stress and shear effects (especially where tissues of differing densities interface), the supersonic shock wave also triggers a cascade of physiological and histological changes. These include axonal, glial, and myelin damage, disrupted axonal transport, activation of inducible nitric oxide synthase, and oxidative stress (Cernak et al., 1999, 2001a, 2001b; Saljo et al., 2000; Povlishock and Katz, 2005; see Anderson, 2008; Elder and Christian, 2009; and Taber et al., 2006 for comprehensive reviews). It is of concern that such abnormalities occur at even modest blast pressures. These effects

[17] More than one mechanism of TBI can occur, as when the individual is exposed to a supersonic shock wave, then struck in the head by a flying object or thrown against a fixed structure. Furthermore, polytrauma is common, with pulmonary damage, penetrating fragment wounds, or crush injuries (Pennardt and Lavonas, 2010). Such factors make it difficult to attribute effects to a single cause.

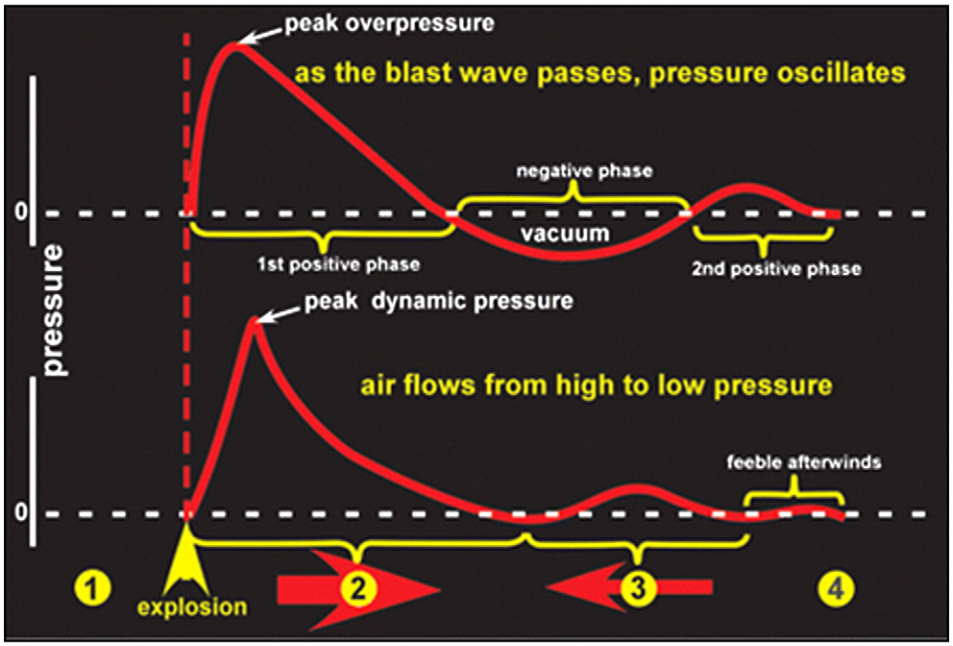

Fig. 6. The sequence of changes in atmospheric pressure (top curve) and wind force (bottom curve) following an explosion that make up the blast wave. Prior to the explosion (1), pressure and wind force are normal. With the passage of the shock front (2), the blast forces are maximal and the wind flows away from the explosion (2, arrow). This is followed by a drop in atmospheric pressure to below normal (3), resulting in the reversed blast wind (3, arrow). Atmospheric pressure and wind force return to normal after the blast wave subsides (4). From Taber et al., 2006, reprinted with permission.

extend beyond the hemorrhage, direct tissue damage, and diffuse axonal injury, which are commonly seen following impact TBI.

In addition, the supersonic shock wave created by a high explosive blast is accompanied by a blast wind (Fig. 6, bottom curve), which can propel objects and people considerable distances. Like the shock wave, the blast wind comprises both positive and negative phases. Due to the unique effects of high explosive blasts, a taxonomy has been developed to distinguish among primary (supersonic shock wave), secondary (object hitting head), tertiary (head hitting object), and quaternary (asphyxia, burns, crush injuries from collapsing building or vehicle rollovers) blast effects (DePalma et al., 2005; Elder and Christian, 2009; Finkel, 2006).

6.3. Blast effects on brain function

There is substantial evidence linking primary blast TBI to neuropsychiatric sequelae; however, there is little information on acute or chronic alterations in cognitive function. Whereas ERPs are standard tools for evaluating functional brain changes, most studies have focused on sensory processing in blast survivors (Lew et al., 2007b). Damage to the auditory system is expected due to the vulnerability of these structures to trauma in general (Duncan et al., 2005) and to blast overpressure in particular (Lew et al., 2007b). Impairment in visual processing is also common after blast TBI (Lew et al., 2009).

6.4. Challenges to research on blast TBI

The paucity of studies can be attributed largely to the difficulty of gaining access to wounded service members, especially those with recent blast TBI. In addition, details of the traumatic event are not always available. The intensity of the blast wave generated by a high explosive depends on factors such as the type, shape, and amount of explosive used. The intensity of the blast wave varies with the distance from the blast and whether it occurs in the open or in the interior of a vehicle or building. Since little or none of this information is available routinely, it is difficult to assess the magnitude of the blast injury. Medical records often do not provide complete information on blast exposure. The tendency for military personnel in a war zone to underreport blast exposure or to minimize its sequelae poses additional complications for research (Kennedy et al., 2007; Lew et al., 2005a). It is especially problematic for studies of mild TBI. A related problem, particularly in mild TBI, is differentiating between symptoms due to blast effects and those due to the stress of battle, the psychological trauma of being wounded and helpless, as well as those due to pain and sleep deprivation (Bryant 2008; Cernich et al. 2007; Elder and Christian, 2009; Ford and Rosenfeld, 2008; Jones et al., 2007).

6.5. Assessment of primary blast TBI

To augment existing clinical information, it has been proposed that more readily reported and accurately documented measures of primary blast TBI be employed. The Glasgow Coma Scale (Teasdale and Jennett, 1974) and the newer Military Acute Concussion Evaluation (Defense and Veterans Brain Injury Center, 2009) are both used routinely in theaters of operation (Elder and Christian, 2009). However, a recent report questions the validity of the Military Acute Concussion Evaluation if it is administered more than 12 h after injury (Coldren et al., 2010). The Ohio State University TBI Identification Method (OSU-TBI-IM; Corrigan and Bogner, 2007), which assesses a patient's prior history of TBI and identifies those with an undocumented TBI, has been adapted to assess blast as well as impact TBI.

Tympanic membrane rupture has also been proposed as an index of blast exposure (Lew et al., 2007b; Xydikis et al., 2007). DePalma et al. (2005) suggested that "rupture of the tympanic membranes serves as a convenient and sensitive marker for blast injury" (p. 1336) and added, "if the tympanic membranes are intact, serious primary blast injuries can be conditionally excluded in the absence of other symptoms" (p. 1339). They also acknowledged, however, that tympanic membrane rupture is not a perfect index of blast injuries, with limitations in both sensitivity and specificity. However, this

measure may offer a conservative inclusion criterion for the presence of primary blast TBI.

7. A next step in TBI research: the "brain indices" study

We have initiated a prospective, longitudinal cohort study aimed at improving our ability to predict posttraumatic stress disorder (PTSD) in service members who have sustained mild TBI. Survivors of both impact-induced and blast-induced mTBI, and, for comparison purposes, service members who have sustained a trauma-related injury with no TBI, are to be assessed over six months. This will enable us to track the development of PTSD and to describe the similarities (if they exist) among prognostic factors in those who develop the disorder. Psychiatric and neurologic evaluations, as well as a comprehensive brain assessment battery, are administered as soon as possible after injury (baseline). Our battery of "Brain Indices" comprises measures of brain structure and function. Brain structure is evaluated using brain MRI and DTI (Basser et al., 1994; Sundgren et al., 2004). Measures of brain function comprise ERPs, neurocognitive measures, and neurological soft signs. Outcome will be evaluated three months after the baseline assessment using the same psychiatric interviews, as well as evaluation of post-concussion symptoms, overall health status, emotional distress, and perceived quality of life. The data will also allow characterization of brain changes following mTBI as a function of impact- versus blast-induced trauma. The full brain assessment battery will be re-administered after six months to explore the course of neurological and neurocognitive impairments associated with mTBI.

8. Concluding remarks

8.1. ERP implications for TBI

With the exception of a modest increase in P3a after orbital frontal damage (Elting et al., 2008), the principal changes in cognitive ERP components following severe TBI can be characterized as "later and/or smaller" (e.g., Campbell et al., 1986; Duncan et al., 2005; Gaetz et al., 2000). This suggests that brain injury, when sufficient in severity, diminishes and delays the available resources necessary to evaluate and monitor both internal and external events and states. Thus, when modifications in behavior are needed, the error signal is more difficult to implement (e.g., Larson et al., 2007a, 2009b; Larson and Perlstein, 2009). From the perspective of cognitive control research, the key terms to describe the normal corrective processes are *evaluate* and *regulate*. Both of these processes appear to be compromised following TBI.

The evidence from ERP investigations suggests that despite apparent recovery, subtle deficits in information processing may persist long after the original brain injury and may not be apparent on standard psychometric tests (Segalowitz et al., 2001). ERPs provide a unique method of monitoring these enduring changes, as well as a measure of treatment effectiveness.

The finding that severe TBI is worse than moderate TBI, which is worse than mild TBI, seems to echo Lashley's (1950) principle of "mass action." Namely, the cognitive deficit following brain injury is proportional to the amount of tissue destroyed. Also, the more complex the task, the more disruptive the lesion, Lashley's other principle of "equipotentiality," appears not to apply to TBI. It states that engrams[18] are distributed throughout the brain, and what matters is the amount of tissue destroyed—not the location. However, the evidence from studies of TBI survivors that examined lesion location via imaging (e.g., Elting et al., 2008; Lombardi et al., 1999; Perlstein et al., 2004; Scheibel et al., 2007; Soeda et al., 2005) points to a critical role of frontal or fronto-temporal structures. Damage in these areas, common after TBI, appears to be more likely to alter ERPs than damage elsewhere in the brain.

8.2. The role of neuroimaging: are ERPs necessary?

When head trauma requires medical attention, providers will often request structural neuroimaging data provided by scanners (CT or MRI). Diffusion tensor imaging (DTI) can also be used to assess cerebral connectivity (Basser et al., 1994). Similarly, when researchers investigating the neurological basis for sequelae of TBI use functional brain imaging, they tend to employ techniques offering high spatial resolution, such as fMRI, PET, or single photon emission computed tomography (SPECT), particularly for subcortical structures. However, these functional imaging techniques—which have a time base in minutes—are not able to capture critical aspects of disturbances in information processing that occur on a millisecond-by-millisecond basis.

Moreover, the two neuroimaging techniques used most often to evaluate TBI, CT and conventional MRI, underestimate brain injury and are poorly correlated with outcome (e.g., Arfanakis et al., 2002; Gallagher et al., 2007; Hurley et al., 2004; McAllister et al., 2001; Neil et al., 2002). The primary reason for this is that neither CT nor conventional MRI sequences detect diffuse axonal injuries, the most common form of TBI (e.g., Bazarian et al., 2007; Capruso and Levin, 1992; Evans 1992; Filley, 2005; Inglese et al., 2005; Levine et al., 2006). Diffuse axonal injuries comprise stretched and injured axons, i.e., the white matter conduction fibers in the brain. Diffuse minor bleeding may escape detection with standard MRI (Bigler, 2004), although it can be seen using susceptibility weighted imaging (Reichenbach and Haacke, 2001).

ERPs offer the fine temporal resolution necessary to capture neural processes that support the cerebral substrates of cognition. Recent advances in ERP technology, such as employing dense electrode arrays that enable topographic ERP data to be back-projected onto the patient's own structural MRI, increase the precision and descriptive value of the method. Comparisons of the TBI survivor's ERP data with normative databases advance the technique from the descriptive to the inferential.

8.3. Information processing

The application of ERPs to elucidate the neuronal damage underlying deficits in attention and cognitive processing subsequent to TBI has shown considerable promise. In fact, a key deficit following TBI is impaired attention. The highly replicated findings with P300 and N2b, prime indicators of attentive capacity (e.g., Näätänen and Picton, 1986; Wickens et al., 1983), indicate that following TBI, processing of information is diminished or slowed, and these effects are accentuated as the task becomes more demanding. This would appear to capture the essence of the ERN, FRN, and slow wave results as well. Although there are some discrepant results, they may be due to differences in methodology, stimuli, tasks, analysis techniques, or heterogeneity of the TBI group. As noted above, what is needed is a standard set of ERP paradigms, so that results can be compared across laboratories (Duncan et al., 2009).

8.4. Cognitive control

Impairments in monitoring and modifying behavior following TBI are assayed by ERN, FRN, Pe, and slow wave (Larson et al., 2007a, 2007b, 2009a, 2009b; Larson and Perlstein, 2009). This fundamental change in behavior is reminiscent of the observations made of brain-injured service members in previous wars (Goldstein, 1942, World War I; Luria, 1948, World War II). Whereas they did not have access to electrophysiological or neuroimaging data, these scientists noted the

[18] Site of memory storage in the brain, based on studies in rats.

incapacity of TBI survivors to cope with even simple decision-making tasks or to plan for the future, and the tendency to repeat errors despite corrective instruction. New technology has helped to specify and delineate the deficits described by these clinicians.

8.5. Future directions

The justification for this research, at least from the point of view of the Department of Defense funding agencies, is not merely to advance basic knowledge of the brain, but to lead to innovative and effective remedial therapies for both service members and civilians. The Brain Indices project (Section 7) relies heavily on ERP data to predict posttraumatic stress disorder and post-concussion symptoms, overall health, and perceived quality of life. Such information can lead to more effective prevention. A second thrust of this project concerns characterization of blast injury.

Epidemiological studies continue to reveal the neuropsychiatric symptoms that may arise after blast exposure in humans. Mathematical and animal models are elucidating pathophysiological mechanisms linking etiology with symptoms. Scores on the Glasgow Coma Scale and Military Acute Concussion Evaluation, as well as tympanic membrane rupture, offer plausible indices of primary blast TBI in humans. Furthermore, there is a battery of ERP techniques available to measure alterations in electrocortical processing associated with specific cognitive deficits (e.g., Duncan et al., 2003, 2005, 2009; Lew et al., 2007a, 2007c; Solbakk et al., 2005).

Despite the substantial value of the enhanced prediction that the results of the Brain Indices study may provide, it is not immediately evident how and whether the ERP findings can be utilized in remediation. It is conceivable that some innovative and improved cognitive retraining program and/or refined behavior modification therapy would take the ERP findings into account (Halbauer et al., 2009). Before this could take place, there would have to be substantial agreement and replication of the findings across laboratories.

Another new direction is the application of state-of-the-art imaging methods (fMRI, DTI, and susceptibility weighted images) to help illuminate and clarify the nature of the lesions. It may be, for example, that the observation of frontal lobe involvement is actually reflective of disruption of a system involving widespread connections from brainstem to frontal cortex, a result that would be consistent with the ubiquitous attentional loss (cf., Mirsky and Duncan, 2005).

The future of ERP research and application, especially to wounded service members, looks especially promising. It is likely that the use of ERPs in evaluating and planning the treatment of TBI survivors will become standard clinical practice.

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