



Electrophysiological markers of cognitive deficits in traumatic brain injury: A review

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ABSTRACT

Event-related potentials (ERPs) and oscillatory activity from the human electroencephalogram (EEG) provides a rich source of data that helps elucidate specific processing impairments in TBI patients. This review will focus on some of the central and disabling cognitive deficits in TBI and how broadband ERP markers and the spectral content of the EEG can help explain abnormalities in brain function that impact upon processing speed, sustained attention, performance monitoring, inhibitory control and cognitive flexibility. Physiological signals also provide useful outcome markers in cognitive intervention studies in conjunction with behavioural endpoints. Potential rehabilitation approaches utilising electrophysiological markers of recovery are also discussed. Progress has been made in recent years in defining key pathophysiological mechanisms in the context of sensitive laboratory paradigms. However, aberrant physiological signals need to be understood more clearly in future studies in terms of the neuroanatomical impact of injury, particularly in relation to the most common type of damage in TBI, disrupting extended white matter fibres.

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1. Introduction

Investigations using electrophysiological methods have developed our understanding of damaged cognitive mechanisms in Traumatic brain injury (TBI). A wealth of analysis techniques, sensitive to the timing of neural activity, has helped elucidate covert abnormalities in brain function associated with overt behavioural deficits commonly seen after TBI. These include behavioural changes in attention, memory, executive function as well as broader personality and psychosocial changes. This review will explain how electrophysiological markers can offer important insights into the nature of cognitive and behavioural impairments seen at clinical assessment and throughout the course of rehabilitation.

Neuroanatomical imaging techniques are evolving and researchers are gaining improved anatomical resolution in the quantification of TBI-related tissue loss. However, in spite of this progress, only generalised whole brain measures of volume loss consistently predict general clinical outcome such as standard neuropsychological performance and information processing speed. More specific brain-behaviour relationships have not been reliably identified perhaps, in part, due to the distributed nature of the neuropathology (Levine et al., 2006). The most common type of damage in TBI is diffuse and occurs to the extended white matter (axonal) fibres, particularly fronto-striatal, fronto-parietal and fronto-temporal path-

ways (Smith et al., 2003). These lesions can result in a range of deficits, some highly specific such as retrograde amnesia (Levine et al., 1998) and others more general, such as those of the attention-arousal system leading to impaired concentration and reduced alertness (Robertson et al., 1997). Recent evidence (Little et al., 2010) points to some specificity of damage at the loci of axonal fibres projecting to and from frontal cortices and thalamic nuclei. Lesions to thalamo-cortical tracts account for considerable variance in executive dysfunction in TBI. By contrast, damage to the cortical frontal lobe structures, cortico-cortico tracts, or corpus callosum alone do not reliably account for these deficits. Although findings such as these are encouraging in terms of understanding more central mechanisms that underlie putative dysexecutive problems in TBI patients, the acquisition of physiological data time-locked to specific behaviours offers a powerful approach that compliments anatomical data. **Event-related potentials (ERPs) and oscillatory activity from the human electroencephalogram (EEG) provide a rich source of data that offers important insights into cognitive processes in the human brain and provide a means of assessing neuropathology. Specific brain systems can be dissociated by these electrical recordings and changes to the component structure of ERP signals can lead to important inferences about the nature of specific processing impairments.**

This review is not an exhaustive account of all electrophysiological markers identified to date but will focus of some of the core disabling cognitive deficits experienced by TBI patients and how cognitive and electrophysiological recordings have elucidated intact and impaired component processes during task performance. Moreover, the utility of electrophysiological signals as an adjunct to cognitive intervention studies will also be discussed.

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2. Processing speed

One of the most generalised impairments following brain injury is reduced processing speed of cognitive operations (Ferraro, 1996; Mathias et al., 2004; Mathias and Wheaton, 2007). It has been demonstrated in a meta-analysis across 13 studies (Ferraro, 1996) that patients with brain injury are 1.54 times slower than healthy controls on measures of simple and choice reaction time. Moreover, speed of information processing is also correlated with executive functioning even when controlling for performance accuracy in TBI patients (Madigan et al., 2000). Slowed processing speed on a range of reaction time tests has been associated with the presence of diffuse axonal injury (DAI) following brain injury and RT is disproportionately slower, in TBI patients than controls, especially on tasks requiring the interhemispheric transfer of information where white matter integrity is essential (Felmingham et al., 2004).

From a clinical perspective, psychomotor function is commonly assessed using RT measures; however, since a patient's reaction time is the combined sum of both input (perceptual) and output (motor execution) processes, it cannot be determined whether the basis of a processing speed deficit is perceptual or psychomotor in origin or indeed both. Recording Event Related Potentials (ERPs) that are both stimulus-locked and response-locked (Lew et al., 2009) circumvents this limitation and offers insight into the impaired neural processing underlying slowed processing speed. Lew and colleagues analysed the RTs and ERPs of TBI patients and controls that completed an oddball discrimination task. TBIs showed longer RTs to targets than controls. Both a stimulus locked ERP component (P300) and a response locked ERP component (Motor Potential, MP) were reduced in amplitude and delayed in latency in TBI patients compared to controls suggesting that, in their TBI sample, both perceptual and psychomotor processes were impaired.

The results of Lew et al. (2009) might imply that generalised slowing of both input and output processes occurs in brain injury; however, under these circumstances it is difficult to discount the possibility that the diffuse nature of TBI has disrupted the physical substrate of ERP generation (i.e., reduced signal quality in general) rather than indexing the specific stages of information processing speed deficits per se. Nevertheless, other research, utilising the precise temporal resolution of ERPs, has revealed differential sensitivity of ERP components to the effects of trauma. Specifically, the evidence suggests that *qualitative* disruption to early perceptual discrimination processes has a downstream effect on the speed of processing by delaying the transfer of information from stimulus processing to response selection. For example, it has been reported (Reinvang et al., 2000) that early processing deficits are apparent in discriminative stimulus processing and termination of irrelevant processing in both active and passive oddball tasks (reflected by reduced N1 and P250 amplitude) in brain injury patients compared to controls. Although, no latency differences were observed in these early ERP waveforms, the later components in the ERP reflecting cognitive operations such as stimulus–response mapping (the N2 and the P300) were significantly later in peak latency in TBI patients compared to controls. This delayed neural processing may be a downstream result of earlier perceptual deficits compromising discrimination of stimulus properties and rejection of irrelevant information. Another study demonstrating qualitative disruption (Heinze et al., 1992) found that longer RTs and longer latency P3 responses were apparent in patients relative to controls in a visual discrimination task. However, disproportionate reductions in amplitudes were observed in intermediate ERP components (N1, P2, and N2) compared to early (P1) and later (P300) waveforms implying differential sensitivity of injury to discrete stages of processing. Specifically, the authors suggest that brain injury impacts upon simple feature registration and early target discrimination as reflected by the reduced intermediate components and this exerts downstream delays

on neural processes linked to stimulus–response mapping indexed by a prolonged P300 latencies in patients compared to controls. However, since P300 latency mainly reflects stimulus-processing time, in contrast to response-processing, its sensitivity as index of any response-time delays in TBI patients is best seen in fast conditions, with its sensitivity decreasing when response times get longer.

A more direct way to assess processing speed deficits in TBI patients that manifest themselves between stimulus decoding and response preparation has come from studies investigating the Contingent Negative Variation (CNV) waveform. The CNV is elicited in tasks that present a warning stimulus (e.g. a tone or visual cue) which forewarns the presentation of an upcoming target that requires a response (e.g. withhold/respond). The morphology of the CNV is first observed after the warning stimulus in which a series of positive and negative polarity shifts over fronto-central scalp are evoked followed by in a pronounced negative signal described as the early CNV. This is followed by a sustained negativity that persists until the presentation of the target – the late CNV. Consistently, TBI patients show longer RTs to the target stimulus than controls (Campbell et al., 1990; Cremona-Meteyard and Geffen, 1994; Segalowitz et al., 1997, 1992). In one of the latter studies (Cremona-Meteyard and Geffen, 1994) participants showed delayed processing of warning cues (increased P2, N2 and P3 latencies) as well as impaired deployment of attention to the warning cue (reduced amplitude of P2) compared to controls. When the cue informed participants to withhold to the subsequent target, patients showed persisting activation of the late CNV suggesting perseverative response activation. In another study examining CNV abnormalities in TBI patients (Rugg et al., 1989) the early CNV following the cue did not differentiate go and no-go trials suggesting a deficit in orientation to the cue information and, again, no attenuation of the late CNV when a no-go stimulus was upcoming. The evidence suggests that the longer response times in TBI patients may occur because of impaired cue processing that, in turn, disrupts communication with responses-end systems. Furthermore, healthy controls show an association between greater amplitude of the late CNV and shortened RTs suggesting the late CNV is a good index of the efficiency of which the response system is activated in the healthy brain. By contrast, TBI patients, in the abovementioned studies (Cremona-Meteyard and Geffen, 1994; Rugg et al., 1989) do not show this relationship suggesting a breakdown in communication between impaired cue processing and carryover delays in response selection and execution.

In contrast to the aforementioned experiments that have used putative input–output paradigms to understand processing speed deficits in TBI, simple and more complex Visual Evoked Potential (VEP) markers, in the absence of response output information, can reveal further information as to the nature of possible information processing deficits in TBI (Lachapelle et al., 2008, 2004). By analysing low-level VEPs evoked by stimuli with an homogenous motion or orientation pattern in comparison to stimuli of greater complexity (i.e. textured stimuli) Lachapelle et al. (2004) found that VEP peak times to homogenous stimuli did not differ between TBI patients and controls but peak times were longer to textured stimuli in TBI patients than controls. These findings suggest that TBI patients show spared first-order visual processing (restricted to area V1 of visual cortex) but impaired higher order visual processing mechanisms that may originate from second-order antero-posterior cortical processes higher in the visual processing chain. Lachapelle and colleagues also stress that these electrophysiological markers may be sensitive to abnormalities in visual pathways as yet undetected by radiological analysis. Moreover, in a more recent analysis (Lachapelle et al., 2008) restricted to TBI patients with mild injury, it was demonstrated that ERPs to textured stimuli as well as visual oddball stimuli were both delayed in peak latencies and associated with greater risk of a negative vocational outcomes. In view of the functional significance of ERP markers of visual processing efficiency they could further

contribute to our understanding of spontaneous or rehabilitative plastic recovery after mild brain injury.

There has been some success in retraining response speed in TBI patients. A study was designed (Deacon and Campbell, 1991) to measure the extent to which feedback and designated time windows for responding, might shorten the RTs of TBI patients and normalise responding. It was also asked whether these benefits would carry-over when these external cues were removed. Patients' RTs became significantly faster and remained faster, at a comparable speed to controls, after the cues were removed. Furthermore, the retrained RTs of patients occurred at approximately the same time as their P300 latencies. However, no alternation of P300 latency was observed as a result of training. Early investigations of the instructional influences on speed and accuracy have also shown that P300 latency does not vary as a function of the directed strategy employed by the subject (Kutas et al., 1977). Deacon and Campbell (1991) proposed that by emphasising speed over accuracy in training may have influenced the patients to abandon their default strategy of prioritising accuracy over speed which might be considered a compensatory strategy to the effects of brain injury. It may be that the cues during training served as a substitute for the inefficiencies of damaged frontal regions in monitoring ongoing performance and exerting control when a change in strategy to initiate increased speed of responding is called upon. It remains to be seen whether qualitative changes in physiological markers of processing speed are influenced by different cognitive strategies employed by TBI patients or fundamental neuroplastic change to damaged systems or a combination of both. These issues have been addressed elsewhere with respect to TBI and cognitive aging in an excellent review (Bashore and Ridderinkhof, 2002). However, a recent study (Izack et al., 2010) reported that TBI patients exhibited a shortening of the P300 peak latency after the administration of cerebrolysin, a neurotrophic factor drug that has been shown to promote synaptic repair in animal models (Sharma et al., 2010).

Through further study of the temporal sequence of ERP components, it may be possible to delineate sub-groups of TBI patients who may have differential impairments in early perceptual processes, stimulus-response mapping or delayed psychomotor processes that account for processing speed prolongation. Moreover, knowledge that the latency of ERP components does not vary with strategic processing changes linked to speed/accuracy trades-offs leaves open the possibility that more fundamental plastic changes affecting neural transmission speeds could be indexed by latency shifts in ERPs. Such approaches would help tailor pharmacological and neuropsychological interventions to suit specific rehabilitation needs for a heterogeneous clinical population.

3. Sustained attention, performance and physiological variability

Many TBI-patients frequently complain that concentrating on mental activities is unusually tiring and demanding. These patients often experience waxing and waning of attention over time leading to significant problems with memory, (e.g. remembering to take medication) and with initiating activities (e.g. reduced initiative to engage socially and occupationally). While information-processing speed may often be associated with the capacity to control attention under these circumstances, it has been demonstrated (Segalowitz et al., 1997) that attentional control and speed of processing may be dissociable processes after traumatic brain injury. Segalowitz et al. (1997) found that performance variability in RT, a reliable index of cognitive stability and frontal lobe integrity (Stuss et al., 2003), was highly related to ERP markers of attentional allocation (P300) and sustained anticipatory control (late CNV waveform). These components predicted 83% of the variance in RT variability after partialling out variance due to response speed. Moreover, slowing of stimulus evaluation times, as indexed by P300 latencies, was not associated with performance variability. The implication of Segalowitz et al.'s (1997) findings are that among TBI participants aspects of attentional

allocation and control that are not processing speed-related may account for an important source of variance in RT and, in turn, may contribute to performance variability which could be a functionally significant factor for everyday problems in TBI patients. Indeed, in our own work, we have shown that TBI patients' errors on a sensitive measure of sustained attention also correlated with everyday reported cognitive failures and variability of response time (Dockree et al., 2006a).

The aforementioned CNV and P300 components are, of course, closely tied to specific stimulus characteristics that are evoked by the task. Insights into the stability of attention and the time course of attention lapses have also been provided by examining induced changes in the spectral content of the EEG. Recent work with healthy controls (Lutz, et al., 2009) has demonstrated that long-term focused attention (FA) meditation training successfully enhances the stability of attention. Three months of FA meditation training had the effect of increasing consistency in the oscillatory phase of the theta band (3–7 Hz) over frontal brain areas and reducing response time variability during a dichotic listening paradigm that required discrimination between target and non-target stimuli. At the end of training those participants who showed the greatest increase in theta band consistency (i.e. a more stable neural response) also exhibited the largest decrease in response variability. Neural and performance stability was not limited to target processing but also distracter processing too, suggesting that training may have helped participants resolve the competition between task-relevant and irrelevant processes. For a more detailed discussion of issues concerning task irrelevant thought, see Smallwood and colleagues (Christoff et al., 2009; Smallwood et al., 2008; Smallwood and Schooler, 2006). Lutz and colleagues argue that increased EEG phase consistency or phase locking may be an important marker for increased cortical signal-to-noise in networks controlling sustained attention. The clinical ramifications of these findings are important for understanding damaged networks in TBI patients where reduced cortical signal-to-noise, disruption of the oscillatory rhythm and increase performance variability may co-occur providing valuable interactive markers. Analysing oscillatory phase activity in TBI patients may prove to be useful in understanding patients' attentional instability and in tracking brain correlates of mental training that serve as reliable endpoints for rehabilitative approaches.

Where Lutz et al. (2009) have focused on how optimal states of attentional stability are achieved in the brain, work in our own laboratory has examined which changes in brain activity can foreshadow transient lapses of attention in the healthy control and brain injured groups. There is a growing body of work suggesting that the half-life of sustained attention failures is apparent over short periods of minutes and seconds (Pardo et al., 1991; Robertson et al., 1997; Weissman et al., 2006). Our research has quantified attentional lapses in go/no-go paradigms where targets are salient but inadvertently and falsely responded to. In this context, we have demonstrated that TBI-patients show pre-target synchronised alpha (~10 Hz) bursts 3.5 s in advance of critical targets; a pattern that is associated with suboptimal attention and is absent in normally performing controls (Dockree et al., 2004). These findings suggest that damage to either intracortical or thalamo-cortical networks after brain injury may disrupt alpha generators that are involved in the deployment of endogenous processes and impair sustained attention performance.

More recently, we have further explored and refined our understating of ERP signals (Dockree et al., 2005) and oscillatory signals (O'Connell et al., 2009) that foreshadow human error. We sought to establish whether lapsing attention produces effects at all stages of stimulus processing, including bottom-up sensory processing or bears only on endogenous, higher order processes. As in previous studies we defined lapses of attention as failure to detect readily perceivable target stimuli. Using a continuous monitoring task in which a stimulus stream flickered at 25 Hz to elicit a steady-state visual-evoked

potential (SSVEP) we demonstrated that SSVEP amplitude, in the periods prior to a target hit and miss, was closely matched indicating that basic visual processing was unaffected by performance. Under these tightly controlled conditions, oscillatory alpha still proved to be a robust signature of inattention becoming increasingly synchronised in a ~20-second period before a lapse of attention occurred. This work raises the possible utility of feedback based on an alpha power threshold that could be used as an early warning system to prevent critical lapses of attention. We have also demonstrated recently that these aberrant trends in alpha oscillations are underscored by down-regulation in a right lateralised network that has been closely linked to the maintenance of an alert, goal-directed state (O'Connell et al., 2010). Our recent work offers a novel approach to analysis electrophysiological markers of pre-lapse activity in TBI patients. By controlling for change in early sensory processing, it is possible to better understand, more purely, how brain injury disrupts higher-order endogenous mechanisms.

In view of the evidence that suggests behavioural and physiological impairments of sustained attention in brain injury it is an imperative that we develop cognitive remediation strategies that help TBI patients recover control during periods of waning attention. In parallel research with adults with Attention Deficit Hyperactivity Disorder (ADHD), who also experience disproportionate fluctuations in sustained attention (O'Connell et al., 2004; Sonuga-Barke and Castellanos, 2007), we have designed an intervention (O'Connell et al., 2008) called Self-Alert Training (SAT) in which participants learned to produce self-generated increases in alertness via on-line changes in electrodermal activity, an index of autonomic arousal. SAT is a technique that is less reliant on external alerting cues (e.g. periodic auditory alerts) and, instead, reliant on self-generated alerting that is linked to a subject's physiological response. Although initially, a participant produces self-generated increases in alertness to a periodic auditory cue, this is later phased out and replaced by the participant's own self-generated command (e.g. an alerting phrase, "wake up"). Training is reinforced via a visual feedback cue conveying the magnitude of each self alert through on-line changes in electrodermal activity (EDA). Comparison of pre- and post-training data showed that SAT was associated with increased levels of autonomic arousal and reduced attentional errors. In contrast, participants in a placebo condition exhibited a steady reduction in arousal over time and no improvement in sustained attention performance.

The use of an alerting technique that is not reliant on particular environmental conditions can provide a highly flexible means of triggering controlled behaviour that is potentially applicable to TBI patients. However, more research is necessary to determine the length and intensity of training necessary to produce lasting benefits from SAT.

4. Performance monitoring and awareness

Repeatedly making the same mistake, such as failing to lock the front door when leaving the house or saying something without realising that it might be taken as insulting, are everyday cognitive failures that are often more frequent after brain injury. Furthermore, habitually resorting to an inefficient or disorganised plan without being aware of the error is problematic in TBI-patients. Impaired awareness of deficits in TBI patients has been identified as a significant factor in determining successful outcome, in terms of rehabilitation (Lam et al., 1988), vocational status (Sherer et al., 1998a; Wise et al., 2005), functional independence, (Trudel et al., 1998) and caregiver distress (Prigatano and Fordyce, 1986). Research in our laboratory has found that TBI participants show reduced error awareness on simple laboratory error detection tasks (O'Keefe et al., 2007; O'Keefe et al., 2004) and are more likely to falsely yet assuredly accept misleading information as the product of 'remembering' (Dockree et al., 2006b).

In these contexts we have shown that skin conductance responses are reduced in amplitude to unaware attentional lapses and to false memories that are subjectively reported to be accurate.

Investigating signals emerging from the broader error-monitoring network will be vital to understanding impaired detection and correction of erroneous behaviours in TBI-patients. Two well-known error-related ERP components – the Error Related Negativity (ERN) and Error Positivity (Pe) – that have clear neurochemical relationships with the mesencephalic dopamine system, are critical indicators of the integrity of error-processing networks (Frank et al., 2007; Franken et al., 2007). It is proposed that the ERN reflects an early action monitoring system perhaps employed to rapidly detect errors prior to conscious processing (Falkenstein et al., 2000). Beyond error monitoring the ERN has also been associated with changing reward contingencies (Boksem et al., 2008; Holroyd and Coles, 2008) and manipulations of response conflict (Carter and van Veen, 2007; Van Veen and Carter, 2002). By contrast, the Pe is more likely to reflect conscious evaluation of the error since participants who are aware of errors elicit a larger Pe amplitude compared to erroneous responses that go undetected (Nieuwenhuis et al., 2001; O'Connell et al., 2007b). Convergent evidence from ERP and functional MRI supports a critical role of medial prefrontal areas, including the ACC, in the generation of these error-related signals (Hester et al., 2005; vanVeen and Carter, 2002). Investigating the neural basis of conscious error detection and how it is disrupted in TBI-patients will provide an important vehicle for understanding broader failures of insight. Progress in this direction has begun by examining error-related ERP signals in TBI patients. Larson et al. (2007) examined error monitoring performance on a modified colour-naming version of the Stroop task in patients and controls. Although no significant between-group interactions were found for RTs or error rates, TBI patients showed an attenuated ERN response compared to controls; however, the Pe response did not differ between patients and controls. This is the first ERP marker that suggests inefficiencies in performance monitoring in TBI patients. Recently it has also been reported (Larson and Perlstein, 2009) that the amplitude of the Pe, but not ERN, was reliably associated with decreased awareness of deficits as measured by discrepancy scores of self and family reports from the Frontal Systems Behavioural Scale.

In related work in neurologically healthy participants we have demonstrated that error-related ERP signals are enhanced if participants are aware of false presses to incongruent or repeated Stroop stimuli (O'Connell, et al., 2007a). An ERN source localised to anterior cingulate regions, was produced both when participants were and were not aware of their error, but the subsequent error positivity (Pe) component was enhanced only when participants were aware of committing an error. These findings, together with those reported by Larson et al. (2007, 2009), tentatively suggest that although pre-conscious action monitoring mechanism may be dysfunctional, TBI patients exhibit normal conscious evaluation after an error is committed as indexed by an intact Pe, at least in the context of high conflict colour-word stimuli. However, it remains to be seen as to whether patients would still show a robust Pe response under conditions that engender attentional drift such as tasks with low conflict demand (e.g. sustained attention paradigms) compared to the relatively high demand conditions where participants have to resolve within trial conflict (i.e. colour-word competition in the Stroop task). Furthermore, Larson and colleagues have recently demonstrated that anxiety and depression in severe TBI patients disproportionately impairs performance-monitoring (Larson et al., 2009a). Specifically, greater negative symptoms were associated with reduced ERN amplitude suggesting that the emotional sequelae of brain injury are an important interactive factor that compromises monitoring efficiency.

It is thought that the ERN/Pe components are generated when a negative-reinforcement learning signal (i.e. failure to receive an expected reward/outcome) is conveyed to the ACC via the mesencephalic

dopamine system (Holroyd and Coles, 2002). Pharmacological studies have clearly demonstrated that dopamine agonists enhance these ERP components associated with error monitoring (de Bruijn et al., 2004) providing a useful marker of a target for pharmacotherapy in TBI. For instance, new compounds used to restore depleted dopamine may normalise ERN amplitude and boost monitoring of error-related behaviour. Further work investigating behaviour and signals emerging from the broader error-monitoring network will be vital to understanding faulty detection and correction of erroneous behaviours in TBI-patients. Moreover, this data is important for establishing different treatment trajectories for rehabilitation (e.g. cognitive training and/or pharmacotherapy) and linking basic cognitive science to tractable everyday problems.

5. Inhibitory control and cognitive flexibility

An important capacity, often compromised as part of the sequelae of brain injury, is response inhibition, the ability to exert inhibitory control over actions by stopping and disengaging particular behaviours. These can range from simple motor responses to more complex affective behaviours such as impulsiveness and related social inappropriateness and temper outbursts (Prigatano and Fordyce, 1986). Focal lesion studies have implicated right inferior frontal gyrus (IFG) as a key structure during the inhibition of responses and task-sets (Aron et al., 2004). In support of an inhibitory role for the right IFG, transcranial magnetic stimulation in neurological healthy participants has revealed that deactivation of the pars opercularis in the right IFG impairs the ability to disengage an initiated action while sparing the initiation of an action itself (Chambers et al., 2006). Beyond these primary mechanisms for inhibition, functional imaging has identified a broader associated network of cognitive control in the context of inhibitory function. In addition to the right IFG, a subcortical region of the basal ganglia, the subthalamic nucleus (STN), is also active during response inhibition, possibly to suppress thalamocortical output (Aron and Poldrack, 2006). In the context of an continuous demand for adaptive top-down control processes through interactions with bottom-up stimulus-driven task demands (e.g. during go/no-go tasks), putative midline-lateral prefrontal interactions have been identified (Fassbender et al., 2009, 2004; Garavan et al., 2002). Within healthy controls, Garavan et al. (2002) have proposed that those individuals who report more self-rated cognitive failures in everyday life depend on a more reactive 'last-gasp' anterior cingulate engagement to inhibit a response. By contrast, those participants who reported less absent-minded activities employed a pre-emptive 'slow-and-steady' right prefrontal pattern of activation to exert control. Theoretical views propose that brain injury may cause a pathological shift from a predictive to a reactive mode of engagement due to timing deficiencies brought about by shearing of white matter connectivity between prefrontal, parietal and cerebella structures (Ghajar and Ivry, 2008).

In the absence of optimal timing to enable prefrontal areas to integrate sensory information with goal representations, frontal regions will operate on a more reactive basis. We have shown that TBI patients perform poorly on go/no-go tasks that build up a strong response propensity (Roche et al., 2004) where participants are instructed to respond to every alternating stimulus but withhold to a repeated stimulus (e.g. X, Y, X, Y, X, Y, X, Y, X, Y). Under these conditions patients made more errors of commission than controls and, within the TBI group, higher numbers of errors were correlated with faster go-trial RTs indicating a speed/accuracy trade off in patients that was not apparent in controls. Faster responding linked to greater errors suggests a loss in the ability to generate and/or maintain predictive states driven by prefrontal mechanisms. Moreover, TBI patients with faster RTs also exhibited more synchronized alpha power over mid-line fronto-central scalp suggesting greater prefrontal down-regulation in these patients. We also found a dramatic attenuation of

the N2 component on no-go trials in TBI patients compared to controls suggesting poor detection of the to-be-inhibited trials. The ensuing P3 was reduced in patients and its peak latency occurred after the mean response time for errors of commission in patients. It is possible that the onset of this component might signal some active response inhibition processes, and that if this onset does not occur within an optimal latency window, the attempted inhibition will fail. Together the evidence suggests inhibitory deficits may arise in TBI patients due to loss of temporal efficiency of predictive brain states that enable timely inhibitory control.

There is also evidence that TBI patients show impairments inhibiting emotional responses. The orbitofrontal cortex (OFC) is critical for the positive or negative reception of the emotional value of our actions. Therefore, during an emotional event the OFC signals either positive or negative feedback to inform as to the consequences of one's actions. Traumatic brain injury commonly affects the most anterior regions of the prefrontal lobes incorporating the OFC and this can give rise to socially inappropriate behaviour because strong emotional reactions may be elicited without regard to possible consequences (Damasio, 1998; Rolls, 2000). These disinhibited responses arise because of failure to suppress or gate emotional reactions due to impaired OFC function. ERPs provide good utility to demonstrate that OFC damage results in hyper-responsive neural signals in other brain regions associated with emotional responses (Rule et al., 2002). Specifically, they showed that patients with orbital frontal lesions exhibited relatively enhanced P3 responses to mildly aversive somatosensory and auditory stimuli compared to healthy controls and patients with dorsolateral prefrontal lesions. Moreover, OFC lesion patients failed to habituate to the stimuli over times unlike the healthy controls. The findings of Rule et al. (2002) provide the first ERP marker of a disinhibited brain responses to emotional stimuli associated with OFC damage and support the theory of regional specialisations within prefrontal cortex. Dynamic filtering affecting multiple aspects of cognitive and emotional function may be differentially sensitive to damage as a result of TBI and can be delineated by electrophysiological methods.

Failure of evaluative and regulatory mechanisms may underpin impairments in the flexible deployment of attention in TBI patients (Perlstein et al., 2006). Perlstein and colleagues have reported impairments in TBI patients when they are required to switch between different instructional task-sets during a cued Stroop colour-word task. Under incongruent conditions patients failed to produce a fronto-central N450 component that is reliable present in controls and source-localised to the ACC (vanVeen and Carter, 2002). The absence of the N450 in patients suggests they were less able to efficiently detect colour-word conflict. Subsequently, a frontal negative slow waveform was attenuated in patients compared to controls and interpreted as a failure to implement regulatory control to resolve conflict during incongruent colour-word pairings. Moreover, it was noteworthy that TBI patients made more incongruent errors than controls, when required to maintain the instructional task-set in working memory over a longer interval before the colour-word stimulus was presented. During a prolonged 5-second interval a left-lateralised frontal negativity associated with cue-driven anticipatory processes was attenuated in the patients compared to controls suggesting poor maintenance of goal representations in working memory. More recently it has also been reported (Larson et al., 2009b) that a centro-parietal conflict slow potential (conflict SP) is reduced in controls reflecting adaptation to or resolution of conflict but the conflict SP was not reduced in severe TBI patients when foreshadowed by incongruent Stroop trials. The implications are that patients are less able to flexibly adjust or efficiently adapt to conditions of conflict. Together these findings support the conjecture that patients are less adept at signalling when adjustments in regulatory control are required and less able to implement control processes in a timely fashion.

6. The nature of cognitive deficits in relation to TBI severity

Traditional measures to assess severity of injury such as the Glasgow Coma Scale (Teasdale and Jennett, 1976) and Post Traumatic Amnesia scale (Levin et al., 1979) are unreliable at predicting chronic cognitive impairments post-brain injury. One study (Sherer et al., 1998b) reports greater severity of injury associated with poorer meta-cognitive awareness albeit in a group of patients who were predominately classified as severe. A more recent study reports that patients' performance on measures of awareness, executive function and implicit processing distinguishes between moderate and severe TBI with those classified as severely injured showing the greater impairments (Morton and Barker, 2010). However, it has also been demonstrated that the removal of accurate injury severity data from a regression analysis in a large sample of mixed-severity patients had only a modest impact on predictive power leaving neuropsychological performance and demographic data accounting for the substantial proportion of the variance in general cognitive functioning at outcome (Kazmark, 1992).

Cognitive testing and electrophysiological analysis provides sensitivity to impairments which are otherwise undetectable by general neuropsychological evaluation and standard MRI. It is noteworthy that studies which have restricted their analysis to mild TBI – where cognitive sequelae are difficult to measure routinely – have nevertheless identified ERP markers of more subtle deficits of visual processing speed (Lachapelle et al., 2008) attention deployment (Dupuis et al., 2000; Gaetz and Weinberg, 2000; Lavoie et al., 2004) and error monitoring (Pontifex et al., 2009). A WHO investigation has reported that 70–90% of all treated for TBI were classified as mild severity (Holm et al., 2005). Although it is important that electrophysiological markers are utilised across all severities of brain injury to understand the diversity of processing deficits, their use in conjunction with cognitive paradigms may be more sensitive to persistent cognitive dysfunction resulting from mild TBI where signs of damage may elude routine assessment.

7. Future directions: electrophysiological markers and neuroanatomical damage

It is clear that in future research the aforementioned aberrant physiological signals need to be understood more clearly in terms of objective and quantifiable measures of neuroanatomical damage as opposed to level of consciousness measurements that have poor prognostic value. One of the most common neuroanatomical impairments present across all severity of brain injury is diffuse damage to the white matter tracts described as diffuse axonal injury (DAI) that is caused by shearing forces inflicted by the trauma (Kraus et al., 2007). DAI can disrupt cortical–subcortical connectivity and lead to pervasive cognitive impairments. Diffusion Tensor Imaging (DTI) has made much progress in understanding TBI white matter pathology (Jiang et al., 2010; Marquez de la Plata et al., 2010). DTI is sensitive to the diffusion of water molecules which in healthy white matter is relatively constrained in its directionality of diffusion. By contrast, following brain injury white matter tracts show less directional organisation due to changes in the axonal integrity brought about by tearing and shearing of fibres or axonal swelling during trauma.

Importantly, it has also been demonstrated recently that as a key DTI metric, fractional anisotropy, normalises after injury, there is an associated lessening of reported TBI symptoms suggesting that white matter normalisation is central to the process of plastic recovery (Mayer et al., 2010). Furthermore, DTI is sensitive where conventional imaging techniques are negative and can detect the full extent of axonal pathologies from cell death to complete recovery (Bigler and Bazarian, 2010). Advances in quantifying white matter damage in TBI offers considerable research potential to allow improved classification of patients into brain injury severity sub-groups without the continued

need to rely on traditional loss of consciousness and post traumatic amnesia reports that are difficult to validate. The use of objective and quantifiable MRI and DTI metrics to assess injury severity will enable a more constrained selection of patient subgroups. In turn, this will allow a more targeted approach to understand cognitive and electrophysiological deficits in an attempt to offset the problem of heterogeneity of damage.

8. Conclusion

Progress has been made in recent years in defining key pathophysiological mechanisms and processes underlying cognitive deficits in Traumatic brain injury. Electrophysiological markers coupled with sensitive laboratory paradigms can reliably predict chronic disturbances that are central to the cognitive sequelae of brain injury. Reduced speed of processing is one of the most pervasive features of brain injury and stimulus and response-locked ERPs have provided a useful approach for establishing which temporal stage of processing has been disrupted. Processing speed prolongation has also been interpreted in terms of qualitative disruption to early perceptual discrimination processes and poor perceptual integration of complex stimuli which both may have carryover delays for response selection and execution. Where training has been employed to normalise processing speed, it remains to be seen whether qualitative changes in ERP markers are influenced by different cognitive strategies or underscored by fundamental plastic changes affecting neural transmission speeds or indeed an interaction between both factors.

Research suggests that aberrant ERP markers of attentional allocation and control in TBI patients are not processing speed-related and may account for an important source of variance that is functionally significant for everyday cognitive problems experienced by TBI patients. Progress has been made in understanding changes in the intensity of attention through investigating oscillatory activity that predicts down-regulation of alert goal-directed states; understanding the breakdown of performance monitoring by dissociating ERP signals associated with impaired error detection and awareness; identifying electrophysiological markers of disinhibition both in the context of action and emotional responses and dissociating impairments of evaluative and regulatory control that reduce flexibility of cognitive control in TBI patients. Finally, electrophysiological markers of cognitive deficits in TBI patients have primarily been utilised for understanding patients' impairments in the context of paradigmatic functions but in the future they should also be investigated in the context of brain correlates of injury severity, cognitive training gains and novel rehabilitative approaches.

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