

Event-related-potential (ERP) markers of traumatic brain injury (TBI) severity and cognitive function – Understanding how the brain works and thinks post TBI

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Abstract

One fact is that other injuries often co-occur with traumatic brain injury (TBI), thus event related potentials (ERPs) elicited using electroencephalography (EEG) machines like NeuralScan by Medeia often reflect the sum of both injuries. The second fact is that cognitive function includes domains from knowledge, attention, memory and working memory, judgment and evaluation, reasoning and “computation” to problem solving and decision-making. The third is that cross-border mental or neurocognitive or non-traumatic brain disorders that exhibit similar symptoms post-TBI will exhibit impairments in similar domains. Therefore, what if observing similar a) altered EEG-functional connectivity in post-TBI as in Alzheimer’s, epileptic seizures, schizophrenia, stroke etc or b) altered network geometries in post-TBI as in CNS tumors, depression etc is the status quo? What if the reason we are not able to identify pathognomic ERP-markers of cognitive impairment post-TBI that are highly specific and sensitive is simply because we are not thinking as the brain does? What if trying to validate ERP markers of TBI-severity and cognitive function post-TBI in the same manner one validates a candidate diagnostic test is what’s wrong in the first place? Is it possible that domain- and symptom-based identification, management and treatment of cognitive-impairments or TBI-severity are the way to go?

Introduction

Three key features influencing traumatic brain injury (TBI), management and rehabilitation outcomes are: a) psychiatric post-TBI sequelae, b) neurological and neuropsychiatric post-TBI sequelae and c) other injuries co-existing with TBI. The prevalence of some of the psychiatric post-TBI sequelae include; depression: 18.5%–61%, mania: 4.20%, obsessive-compulsive disorder (OCD): 1.6%–15%, posttraumatic stress disorder (PTSD): 3%–27.1%, psychosis: 0.7%, alcohol-related disorders: 34.9%–51%, and that of personality changes like, apathy: 34.5%, affective lability: 5%–32.7%, aggression: 16.4%–33.7% [1-11].

Computerized tomography (CT) imaging of individuals with depression following TBI exhibited decreased bilateral hippocampal and left prefrontal grey matter volume and lesions in the left frontal, dorsolateral and basal ganglia [12-15]. Subjects with mania post-TBI had seizures and showed temporal basal pole lesions [16-18]. Individuals with OCD following TBI showed damage in the orbitofrontal and cingulate cortex and caudate nucleus [19-21]. Similarly in cases of PTSD post-TBI cerebrospinal fluid (CSF) of S-100B levels increased [22]. Psychosis post-TBI with frontal and temporal lobe damage had electroencephalography (EEG) abnormalities; seizures and cognitive impairment was global [23-27]. Individuals with alcohol-related disorders post-TBI showed generalized brain atrophy, reduction in prefrontal cortical (PFC) volume and EEG studies revealed changes in their event-related potential (ERP) patterns; however these patterns returned to no-alcohol-consumption post-TBI patterns if individuals observed abstinence from alcohol (28-30). Personality changes like apathy seen in individuals post-TBI was characterized by subcortical damage while those with, affective lability and aggression exhibited frontal lobe damage [11,28-33].

Neurological and neuropsychiatric post-TBI sequelae seen include neurodegenerative diseases (Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS)), attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and schizophrenia [34-45]. The homology between TBI and its psychiatric, neurological and neuropsychiatric post-TBI sequelae has been found to extend from its symptoms, to cortical regions involved, to *functional connectivity and synchronization of EEGs to exist between genomic signatures (in a landmark study in 2017)* from blood and brain (Figure 1a) [46]. The study used a rodent TBI model to illustrate how TBI imposed a predisposition to the post-TBI psychiatric, neurological and neuropsychiatric sequelae seen. The finding was that TBI affected gene regulatory mechanisms (key driver (KD) genes) involved in cerebral homeostasis influencing epigenomic programming, splicing and transcription factors, and novel network regulators. Simply put, TBI affected KD genes adversely resulting in an increased predisposition to developing ADHD, ASD, PD, AD, PTSD, epilepsy/seizures, stroke, depression and schizophrenia post-TBI.

Another confounding factor in most TBI studies is that while most TBI studies compare healthy controls versus those with TBI, none clearly stipulate that individuals with only TBI and no other general injury were studied [47]. However, it is natural that cortical EEG, qEEG patterns would reflect the sum of both TBI and general injuries an

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individual has sustained or is recovering from as illustrated in (Figure 1b).

Post-TBI symptoms experienced by individuals with TBI range from mild to severe range from nausea, confusion, dizziness, blurred vision, headaches, agitation, to mood changes while neurocognitive impairments range from memory, attention, executive functioning, to processing speed [48-53]. These symptoms can persist from a few days, weeks, months, and years to a lifetime [48,49]. There are tests to assess post-TBI symptoms due to moderate and severe TBI [54-59]. Mild TBI still poses a problem as its symptoms manifest later in certain instances or are transient, nevertheless the symptoms can affect the quality of life, education, employment, performance, the social and relationship domain and in some cases even endanger life [48,49].

However as early as 1993 it was clearly established that post-trauma consequences of mTBI were not always mild and that electrophysiology (EEG) could contribute significantly to a better understanding, management and treatment of the same [50]. In instances where impairments require more sensitive and fine-grained tests using EEG and event-related potentials (ERPs) could provide an endogenous viewpoint of cognitive processes and changes in cortical function, aspects that imaging cannot capture. In this context the present paper examines if domain- and symptom-based EEG and ERP markers of cognitive-impairments or TBI-severity using EEG machines like NeuralScan by Medeia would be a more appropriate approach.

Auditory evoked potentials (AEPs)

The cognitive domains memory, attention, and processing speed are most commonly affected following TBI [51-53]. Alterations/ impairments in these domains can be accessed via the neural correlates of the auditory system to which they are innately intertwined via AEPs [54-61]. Figure 2a presents the AEP components (adapted from Gaetz & Bernstein, 2001) that include early AEPs (auditory brainstem response (ABR), complex ABR (cABR)), auditory middle latency response (AMLR), and auditory late latency response (ALLR) [51,62]. Figure 3 presents an illustrated example of how AEPs can be recorded using EEG machines like NeuralScan.

Among click-evoked ABR studies; latencies and amplitude of waveforms-I, -III, and -V were similar for mTBI (n=19) and no TBI (n=29) in a study by Gallun *et al.*, concussed (n=11) showed a delayed wave-III latency versus control (n=12) participants and reduced inter-peak latency difference was seen in mTBI (n=15) versus 35 controls [63-65]. FFR a component of the complex ABR was reduced and slower responses to fundamental frequency (F₀) and poor pitch coding was seen in concussion (n=20) versus control (n=20) participants in a study by Kraus *et al.* [66].

In terms of click-evoked ABR and AMLR studies: Munjal, Panda, and Pathak studied 50 controls versus mTBI=100, moderate TBI=150, severe TBI=40 [67]. With severity of TBI wave-latency and I-V inter-peak latency of ABR increased while AMLR's showed decreased amplitude of Na and Pa components [66]. Soustiel *et al.* found prolonged Na and Pa waveforms in 15 of the 40 mTBI participants versus 23 controls, while Drake *et al.* found prolonged latency of Pa and reduced amplitude of Pa and Na waveforms in 20 participants with mTBI versus 20 controls [68,69]. A pulse-evoked AMLR study by Arciniegas *et al.* on mTBI=5, moderate TBI=6, severe TBI=9 versus 20 control showed significant differences in P50 amplitude and P50 ratio between mTBI and controls [70].

1a: Overlapping genes between TBI hippocampal signatures or KDs and human GWAS genes of brain disorders

Meng, Q., et al (2017). Table1

GWAS disease	Overlapping gene in TBI hippocampal signature
Alcohol consumption/dependence	CUX2; SLC26A4; ZDHHC21; ESR1; SERINC2
AD	APOE; NMU; PCDH11X; PPP1R3B; PROX1; SCARA3; SMC2; TLL7; ADAMTS9; ARHGAP20; CAMK4; ELMO1; LIPC; PDE7B; PLEKHG1; SP6
ADHD	BCL11A; CDH13; LRRK7; LYPLAL1; NR4A2; SEMA3A; TCEB1; TGFBR2; TSHZ2; ZK5; PAWR; NDN; ESRBB; ADAMTS2; LRRN3; TYRPI
Bipolar disorder	ANKK3; COLEC12; DGKH; DPP10; IRF2BP2; ITIH3; MRPS23; MS2; NFA; PDE10A; PCMS; PPM1M; SIAE; SP8; TTC39B; UACA; CGNL1; DMTF1; FAT4
Bipolar disorder and schizophrenia	ARC; ATP6V1B2; BA11; CACNA2D1; CMYA5; COMMD10; CST7; CTNND2; DDX52; DMD; HACE1; IRK1; KAT2B; MRV1; MYO1E; PRKCQ; PITPNR2; SIM1; SLC39A12; TMEM212; TTC39B; VPS13C
Brain connectivity	CNTN4; EPHA7; NEDD4
Brain structure	BOK; CADPS2; GRIN2B
Cognitive function	PITPRQ; AFAP1L2; CDH13; FAT4; GABRG2; GRIN2B; HCCS; IMMP2L; IRX1; IRX2; JUN; KIAA1217; KLHL1; LHX2; LIPC; MCTP2; NR2F2; PLCB1; RIT2; TOK; TSHZ3; UNC13C; VANGL2; ZNF788; LMO4
Word reading	NOS1AP; TACSTD2; TYRPI
Working memory	CLDN1; DRD2; LPHN3
Conduct disorder	C1QTNF7; MCTP2; NR2F2; RIT2; ST8SIA4; ZBTB16; KCNAS; PDE10A
Eating disorders	CAMK1D; DLGAP1
Hippocampal atrophy/volume	APOE; COL18A1; F5; MAGI2; MAL2; DPP4; MSRB3
Intelligence	CNTN4; COL1A2; GYPC; KIF16B
Major depressive disorder	ADCYAP1R1; CND2; CDH9; EMP1; GRIN2B; HAPLN1; HOMER1; IGFBP3; KCNHS; NDEP2; NEUROD6; PCLO; RASGEF1B; ATP6V1B2
Parkinson's disease	BMP4; DLG2; GPRIN3; RIT2; RORA; SEMA5A; STK39; VPS13C; WNT3
PTSD	COBL; PCSK2; PRKCA; SLC4A5
Schizophrenia	ANKK3; BMP7; CDH13; CXCL12; GNAL; NRGN; PCDH20; PDC; PTGS2; RORA; SNX7; TCF4; VPS13C
Smoking behavior	BDNF; CHRNA3; CHRNA5; KCND2; MAOB; PDE1C

1b: Spectral maps showing P300 response to the oddball target tone

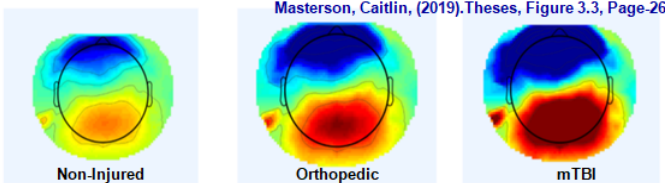


Figure 1. Factoring in Homology and the other-injury factor when looking for markers of TBI- and neurocognition [46,47]

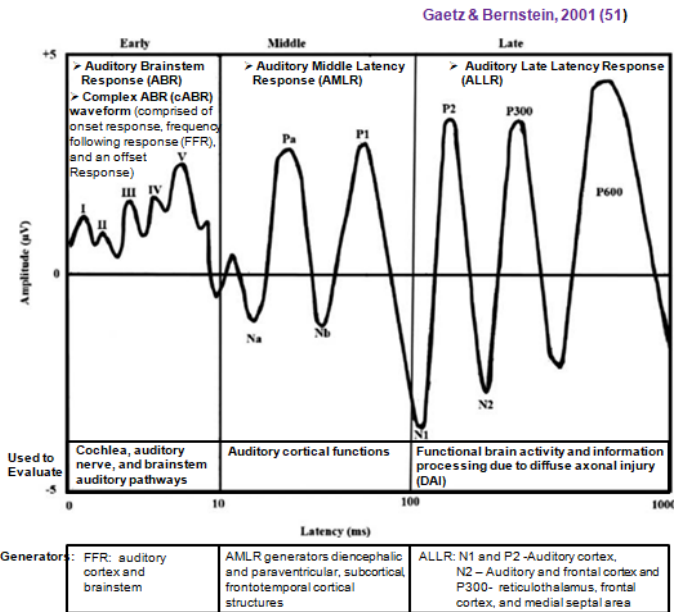


Figure 2. Auditory evoked potentials (AEPs)

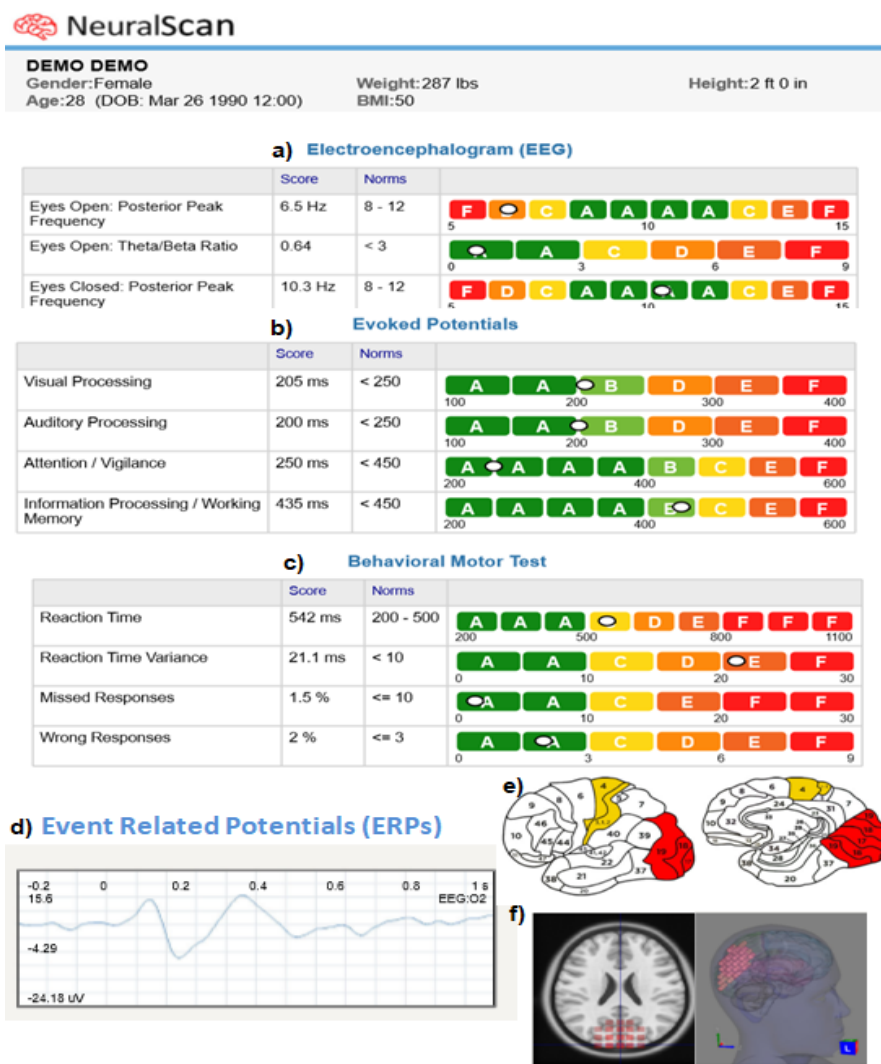


Figure 3. Illustration of AEPs, VEPs, and cognitive function captured using NeuralScan by Medeia.

a) 19-channel EEG (not shown) Resting EEG capturing ability (eyes open, eyes closed condition), missed and wrong responses, b) Evoked potentials: VEP, AEP, Attention, Working Memory. c) Reaction-time (RT), RT variance (RTV), Fi d) Event related potentials (ERPs), e) identification of Brodmann areas affected and f) source location using LORETA

AERPs evoked using auditory oddball tasks showed overall prolonged P3 latencies and reduced amplitude of N1, P2, and P3 waveforms in concussed (n=40) groups study by Gosselin *et al.* [71]. However, smaller P2 amplitudes were seen in 20 symptomatic versus 20 asymptomatic collegiate athletes versus 20 control participants. Solbakk *et al.* observed reduced N2 and P3 amplitudes in mTBI (n=15) participants versus 13 controls [72]. Decrease P3b amplitude with increased latency was observed by Pratap-Chand *et al.* in 20 participants with mTBI versus 20 matched controls [73]. Segalowitz *et al.* used four auditory oddball tasks to elicit AERPs [74]. Reduced amplitudes of P3a and P3b were observed in 10 participants with mTBI versus 12 controls. High school athletes (n=30) were studied by Thériault *et al.* [75]. Smaller P3a and P3b amplitudes were observed in both recently concussed (n=10) and late concussion (n=10) athletes versus controls (n=10). Further late concussed had larger P3b amplitude versus recent concussed i.e. though they appeared to function normally endogenously their neuronal function had altered at the sub-clinical level.

Another study where AEPs evoked using standard and target stimuli were recorded in 19 healthy, 17 with mTBI at 7 days post-TBI

and 17 mTBI both at 7 days and 2–3 months post-TBI also showed prolonged P300 latency at 7 days which appeared to improve at 2–3 months [76]. In terms of cognitive domains these studies found that memory processing and frontal lobe efficiency were affected by decline in attention resources as a result when novel stimuli were presented the response/reaction time was altered which resulted in the chronic motor and cognitive changes seen post-TBI. Similar findings were seen in another study of 24 individuals with mTBI versus 24 healthy controls P3a was more negative following a three-stimulus AEP task [77]. P3a and P3b decrease in amplitude and latency was also seen in another on 40 healthy former athletes in late adulthood, 19 of which had had mTBI in early adulthood while 21 had no history of TBI [78]. Preventing a general consensus is that while several studies have demonstrated delay in latencies for waves-I, -III and -V in mTBI versus controls there are others have reported no difference between controls and individuals with blunt head trauma/soccer players/boxers/athletes [68,79–90].

Visual evoked potential (VEP)

Following mTBI individuals often vision related issues like oculomotor and accommodative dysfunctions, binocular vision

deficits, compromised visual field sensitivity, deficits in binocular vision, visual memory, visual attention, perception and visual information processing [91,92]. Vestibular spatial localization errors, and visuomotor coordination impairment are also common [7,8]. More importantly oculomotor deficits are not self-resolving as other TBI injuries and often require oculomotor-based vision therapy [93-95]. 90% of individuals following mTBI suffer from oculomotor dysfunction. oculomotor dysfunction, 10-40% accommodative deficiencies and 50% light sensitivity that affect fine binocular oculomotor coordination as one scans across a line of text, textual clarity and limits reading duration and comfort and one's maximum respectively [96-101].

In a multimodality-evoked-potential (MEP) prospective study of 18 mTBI subjects VEP was carried out at 2-weeks post injury (Figure 3 presents results of VEPs recorded using EEG machines like NeuralScan). P100 showed no difference beyond 3SD (standard deviations) [102]. Pattern reversal visual evoked potentials (PR-VEPs) recorded in 20 controls and 50 mTBI subjects on days-1 and -30 post-trauma While subjects had no visual complaints and P100 amplitude and latency showed no significant differences between groups, the latency declined and amplitude increased significantly when mTBI on day-30 was compared with day-1. These findings highlight the usefulness of the P100 in detecting sub-clinical visual changes post-TBI [103]. On a study of the organic basis of persistent post-concussion syndrome, latency was beyond 2.5 SD in 30% of mTBI and P100 amplitudes declined significantly when compared to controls [104]. In a study evaluating the long-terms effects of sport-related concussion 18 with history of concussion and 18 controls were evaluated using pattern-reversal VEP tasks. Subjects $\approx$ 6.7 years post-BI, exhibited reduced P1 amplitude independent of duration post injury and the number of injuries. Further sensory-mediated response inhibition (Erickson flanker task) tasks showed that P1 amplitude and P3 amplitude and latency (attention) were significantly related in healthy controls but not in mTBI. For post-TBI subjects P1 amplitude was inversely related to the number of errors of commission but this was not observed in controls. Decline in efficiency of sensory capture could have caused this deficit in attentional resource allocation and inhibition seen [105].

Studies aimed at determining markers capable of differentiating between mTBI and no-TBI or markers to help track recovery were also carried out. Pattern VEP testing was carried out in a study that looked at the response of individuals with mTBI (1-10 years post-injury, n=19) versus visually-normal (VN, n=20) and the degree of luminance (baseline luminance versus luminance reduced using neutral density-ND filters:0.5, 1.0, 1.5, 2.0 and 2.5). Overall, in both groups mean VEP amplitude declined ($p<0.05$) and latency increased ($p<0.05$) with the degree of luminance. At each luminance level the mTBI group showed significant amplitude reduction ($p<0.05$) and latency increase ($p<0.05$) when compared with the VN group. These findings suggest that individuals with mTBI can be differentiated from VN using VEP and the degree of luminance and should ophthalmological rehabilitation be considered the same can be used to track recovery [106]. Another study evaluated visual attention changes using VEP in individuals with mTBI alone (n=5) and in those with self-reported attention deficit hyperactivity disorder (ADHD, n=11) following mTBI. Visual attention changes using VEP alpha band attenuation ratio (AR, both individual and combined alpha frequencies) was evaluated using a) pattern VEP; b) eyes-closed; and c) eyes-closed with number counting. While AR was normal in individuals with mTBI alone it was abnormal in those with mTBI+ADHD. This let Yadav *et al.* to conclude that AR could be used to identify individuals with ADHD post-mTBI [107].

12 adults with mTBI and 12 VN individuals were provided with 'precision tint lenses', and intuitive colorimeter system, visagraph and VEP amplitude and latency were recorded [23]. Few significant differences were seen in reading and VEP parameters suggesting that tinted lenses might be a first line measure to relieve initial discomfort prior to long-term strategies like vision therapy [108]. A texture segregation VEPs (tsVEP) study on 13 individuals with mTBI and 13 controls found that tsVEP peaks increased in individuals with mTBI compared with controls while low-level VEPs (lIVEP) remained within normal patterns. The inference was that tsVEP elicited after lIVEP (around 100 ms) and prior to 300 ms could be used to detect damage to complex visual pathways that are neuroradiologically silent [109].

In a study evaluating convergence insufficiency in normal patients versus post-mTBI subjects were exposed to sustained stimuli (2-rev/s, 85% contrast checkerboard patterns of 1- and 2-degree check sizes) and transient stimuli (4-rev/s, 10% contrast vertical sinusoidal gratings with column width of 0.25 and 0.50 cycles/degree) [110]. Two models were compared (one from a priori clinical study and one derived using study data) for their discriminatory ability between individuals with convergence insufficiency with and without mTBI and had an accuracy of 76% and 86% respectively. The resultant receiver operating characteristic curve for the new model had a sensitivity of 0.92, specificity 0.80 and area under the curve (AUC)=0.857; $p<0.01$ [110]. In a case study on neurophysiological and cognitive functions post sport-related mTBI (8-year old, female, soccer injury) VEPs recorded at 7 weeks pre-injury and 24 h, 7, 22, 32 and 55 weeks post-injury were analyzed [111]. At 24 h post-TBI attention-related cognitive impairments manifested some of which resolved within 22 weeks. VEPs and spectral analyses 1-year post-mTBI indicated cognitive impairments in the vigilance and attention, domain that also impacted on school performance.

Broglio *et al.* studied 44 individuals without TBI and 46 with previous mTBI using ImPACT and ERPs using three-stimulus oddball task. While groups did not differ in their ImPACT scores N2 and P3b amplitudes declined significantly in those with a history of TBI. They concluded that persistent impairments in the domains of attention suggest that one could no longer characterize mTBI a transient with short-term cognitive impairments instead one could not predict which neuropathologies would clinically persist or manifest at a later time point [112].

In two successive studies Gosselin *et al.* examined the root cause of persistent symptoms post-TBI [113,114]. Using functional magnetic resonance imaging (fMRI), blood-oxygen-level-dependent (BOLD) signal changes and ERPs they compared 14 mTBI subjects with 23 controls [113]. fMRI findings were positively correlated while BOLD signal changes and N350 amplitude were inversely correlated with symptom severity. In a subsequent study Gosselin *et al.* study working memory (WM) performance following mTBI (n=44) and 40 controls. Amplitude and latency of frontal (N200 and N350) and parietal (P200 and P300) were studied. Groups did not differ by ERP latency [114]; however, mTBI had significantly smaller N350 and P300 amplitudes, slower reaction times, worse accuracy and a lower percentage of correct answers than the control group ($p<0.05$). They reported that given current follow-up testing for mTBI clinicians may fail to detect and therefore treat consequences of mTBI especially if sub-clinical cerebral/cortical dysfunction existed.

Lachapelle showed that selective deficits in complex visual information processing in individuals with symptomatic mTBI could interfere with vocational outcome [115]. Pattern-reversal, simple

motion, texture segregation and cognitive oddball paradigms were studied in 17 individuals with symptomatic mTBI and 15 controls. mTBI had significantly lower amplitudes, and prolonged latencies for cognitive paradigms and tsVEP ($p < 0.05$). In contrast Di Russo studied ERP (elicited using Go/No-Go task) changes following injuries due to professional boxing and fencing versus non-athletes [116]. While attention and motor response control improved in fencing, cumulative injuries to the head due to boxing resulted in prolonged and decreased P300. Another study on 20 college contact sport athletes also had similar results with marked decline in P300 amplitude attributed to the attention-cognitive domain [117].

The N-back working memory test was performed on 3 different visits on 11 mTBI patients and 7 controls, on three different visits. P300 amplitude and latency revealed that latencies were significantly shorter in controls at every visit while the mTBI group did not show any such improvement. The finding reiterated the persistent nature of mTBI symptoms [118]. Potter *et al.* demonstrated that to achieve an equivalent performance as controls the mTBI group allocated greater attention resources. The mTBI were as fast as controls for the computer-based Stroop tasks but they made more errors. The mTBI group for the card-based Stroop congruent and incongruent tasks were slower and made even more errors and had greater negativity in latency (350 to 450 ms) for the incongruent tasks (greater allocation of attention resources) than to the congruent tasks [119].

Conflict monitoring and adaptation (N450 and conflict SP ERP components) were studied Larson *et al.* in 29 mild TBI and 36 control using Stroop tasks (50% congruent and 50% incongruent trials). Findings were that normal conflict SP sensitive to conflict adaptation in healthy individuals declined in individuals with mTBI resulting in mTBI individuals exhibiting intact conflict monitoring, but altered conflict adaptation and adjustment processes [120]. Larson *et al.* also found comparable performance of mTBI ($n=36$) to controls ($n=46$) in certain aspects of cognitive control. The group measured error-related negativity (ERN), post-error positivity (Pe) components, behavioral (response times [RT] and error rates) following a modified color-naming Stroop task [121].

ERPs pertinent to cognitive and social function following TBI

Cognitive function encompasses processes, including knowledge, attention, memory and working memory, judgment and evaluation, reasoning and “computation”, problem solving and decision-making, comprehension and production of language. Social function includes; personality, thinking, behavior and perception of social cues. Both cognitive and social function can be impaired following TBI [120,122-131]. Among them reduction in processing speed, memory, inability to sustain attention and engage socially are common cognitive impairments seen [12,13,132]. Affecting both personal and social performance is other cognitive failures TBI subjects often report facing in their everyday life. These range from repetitive mistakes to inhibition control and lack of awareness both of which can result in impulsive and socially inappropriate behavior [133-136]. Following TBI impairment in word retrieval is often seen particularly among athletes which effects both every day and official communication [137-140].

For instance among studies on ERPs, cognitive function and outcomes following TBI, Shah *et al.* found elevated frontal midline theta power and reduction of frontal beta power a pattern that correlated with executive attention impairment ($r = -0.67$, $p < 0.001$) in TBI subjects [141-143]. These patterns are attributed to the destruction of afferent nerve connections and inhibition due to hyperpolarized

neurons a condition caused by temporal absence of excitatory synaptic activity (disfacilitation) of the medial frontal neuronal population [141]. Another study looked at working memory (WM) using continuous performance task (N-back) at 5-days, 2-weeks, and 1-month post-mTBI [143]. Arakaki *et al.* found subjects with mTBI patients had increased frontal event-related desynchronization (ERD) at 5-days and 1-month, (Visit-1 and Visit-3) for induced alpha power. For evoked alpha, mTBI patients had lower parietal ERD/event-related synchronization (ERS) at the second and third visits [143]. In the area of cognitive rehabilitation, Porter *et al.* carried out a 3-month cognitive intervention program [144,145]. TBI subjects showed significant improvements in their composite cognitive score and the right inferior frontal gyrus showed significant decline in functional connectivity.

Table 1 presents a rapid yet brief review of ERPs pertinent to cognitive and social function following TBI [146-201]. Figure 3 captures how ERPs pertinent to attention, working memory can be recorded using EEG machines like NeuralScan.

Conclusion - the “third” fact

Cross-border mental/neurocognitive/non-traumatic brain disorders that exhibit similar symptoms post-TBI will exhibit altered EEG patterns in similar domains. AD, PD, ALS, ADHD ASD and schizophrenia are examples of some of the post-TBI sequelae seen [34-44]. Many of these disorders not only share symptoms but a review carried out in 2015 by Rapp *et al.* on EEG and quantitative EEG (qEEG) and event-related potential (ERPs) studies to detect TBI showed similar altered functional connectivity, network geometries and synchronization of EEGs [45]. The findings led to the inference that while distinguishing between TBI and healthy controls was possible it would be difficult to distinguish between psychiatric, neurological and neuropsychiatric disorders that either shared symptoms with TBI or were the post-TBI sequelae observed (Table 2) [45,158,190,202-233]. A genetic study illustrated that these alterations in functional connectivity and synchronization of EEGs key drivers occurred due TBI's affect on key driver (KD) genes and in turn gene regulatory mechanisms involved in maintaining brain homeostasis from transcription factors to novel network regulators (Figure-1a) [46]. It induced DNA methylomic changes in the hippocampus and leucocytes.

Considering the

- inherent overlap and homology between TBI and its psychiatric, neurological and neuropsychiatric post-TBI sequelae,
- the infinite types of TBI, each injury can activate different pathophysiological processes, recovery can also vary in duration, outcome and post-TBI sequelae can also vary.
- differences in demographic characteristics of TBI subjects

attempting to validate “specific” ERP markers of TBI-severity and cognitive function post-TBI is perhaps what's wrong in the first place. For reasons mentioned above while differentiating between a healthy control and a TBI subject might be possible differentiating between symptoms post-TBI and neuropsychiatric may be difficult. For the same reasons looking for “specific” EEG/ERP markers may be akin to looking to looking for the “unnatural”. However, if one instead looks for domain- and symptom-based markers using EEG machines like NeuralScan one may be able to achieve clinical goals and better characterize, manage and treat each TBI injury and post-TBI sequelae. In layman's terms we could be able to understand how the injured brain, heals, responds to treatment, recovers, works, and thinks post-TBI.

Table 1. ERP markers of cognitive and social function in TBI subjects (Adapted and modified from Dockree *et al.* [195])

Cognitive Function	Particulars
Processing Speed	Paradigms to assess processing speed - Using stimulus-locked and response-locked ERPs - RT delays in TBI patients best seen in fast conditions, with its sensitivity decreasing when RT gets longer. - Contingent Negative Variation (CNV) waveform: elicited using a warning stimulus (e.g. a tone/ visual cue) followed by a target requiring a response (e.g. withhold/respond). Results of studies assessing processing speed - Meta-analysis of 13 TBI studies showed individuals with TBI are 1.54 times slower than healthy controls [39]. - Reaction time (RT) is the sum of both input (perceptual) and output (motor execution) processes. Slowed processing speed and RT associated with diffuse axonal injury (DAI) especially seen in tasks requiring inter-hemispheric transfer of information where white matter integrity is lost/threatened [146]. - Stimulus locked P300 and a response locked Motor Potential (MP) are reduced in amplitude and delayed in latency in TBI patients compared to controls [147]. Early perceptual discrimination processes (N1, P2/P250 and N2, amplitude) reduced resulting in delay to the transfer of information from stimulus processing to response selection (N2 and P300) causing significantly prolonged peak latency in TBI patients compared to controls [148] Longer RTs and longer latency P3 responses in TBI patients compared to controls [149]. - Early CNV following cue did not differentiate go and no-go trials. Impaired cue processing might be the cause of longer RT in TBI patients compared to controls [150-153] Retraining/treatment for response speed in TBI patients - Feedback and designated time windows for responding used to shorten the RTs of TBI patients and normalize responding [154]. Patients' RTs speed remained comparable to controls even after cues were removed [154]. Retrained RTs occurred at the same time as their P300 latencies with no alternation of P300 latency. Emphasizing speed over accuracy in training may have caused patients to abandon their default strategy of prioritizing accuracy over speed (a compensatory strategy following TBI) [154]. - P300 peak latency was also shortened after the administration of cerebrolysin (neurotrophic factor drug that promote synaptic repair in animal models) [154].
Sustained attention, performance and physiological variability	- Performance variability in RT (indicator of cognitive stability and frontal lobe integrity) highly related to P300 (ERP marker of attentional allocation) and late CNV waveform (ERP marker of sustained anticipatory control) [151,152,155]. - RT Variance that is attentional allocation related is separate and distinct from RT variance that is processing speed-related seen in TBI versus control subjects [151, 152]. - RT and errors in sustained attention tasks both correlated with everyday reported cognitive failures [156]. - Following TBI reduced cortical signal-to-noise, disruption in oscillatory rhythm and increase performance variability co-occur in damaged networks controlling sustained attention and could serve as potential markers [157]. - Suboptimal attention post-TBI is marked by pretarget synchronised alpha bursts 3.5 seconds in advance of critical targets; this pattern is absent in controls. Damage to intra/thalamo-cortical networks following TBI might disrupt alpha generators pertinent to sustained attention performance [158]. - Steady-state visual-evoked potential (SSVEP) studies indicated that while basic visual processing was unaffected by performance, oscillatory alpha proved a robust marker of inattention (becoming increasingly synchronised before a lapse in attention occurred). The finding indicates that using an alpha based feedback system as an early warning system of critical lapses of attention has potential and oscillatory signals [159-163]. Alpha oscillations could also be used to identify an alert, goal-directed state [159-163]. Retraining Attention control in TBI patients - Long-term (3 months) focused attention (FA) meditation training successfully enhanced the stability of attention [157]. Its increased consistency in the oscillatory phase of the theta band over frontal brain areas and reducing RT variability during a dichotic listening paradigm that required discrimination between target and non-target stimuli. - Another option comes from research on Attention Deficit Hyperactivity Disorder (ADHD) where sustained attention is also challenging [159-163]. Self-Alert Training (SAT), where self-generated increases in alertness is reinforced via a visual feedback cue conveying the magnitude of each self-alert through on-line changes in electrodermal activity (EDA). Initially self-generated increases in alertness is achieved via a periodic auditory cue which is later phased out/ replaced by the participant's own self-generated command (e.g. an alerting phrase: "wake up") [164]. Pre- and post-training data showed increased levels of autonomic arousal and reduced attentional errors in SAT group while the placebo group showed reduction in arousal and no improvement in sustained attention performance.
Performance monitoring and Awareness	- TBI subjects exhibit reduced error awareness on error detection tasks [165,166] - TBI subjects more likely to accept misleading information as 'remembering'[167] - Signals emerging from the broader error-monitoring network are vital to understanding impaired detection and correction of erroneous behaviors in TBI-patients. Error Related Negativity (ERN) and Error Positivity (Pe) neurochemically linked with the mesencephalic dopaminesystem, are critical indicators of the integrity of error-processing networks [168,169]. - ERN reflects an early action monitoring system, it detects a) errors prior to conscious processing, b) changing reward contingencies and c) manipulations of response conflict [170, 171]. - Pe reflects conscious evaluation of error [172,173]. - ERN produced both when participants are aware/unaware of their error, but error positivity (Pe) is enhanced only when participants are aware of committing an error. - 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 [172]. - Medial prefrontal cortical (PFC) regions including the anterior cingulate cortical (ACC) regions are involved in the generation of these error-related signals [174,175]. - Error monitoring performance using colour-naming version of the Stroop task showed ERN response was reduced in TBI subjects compared to controls [176-181] - Amplitude of the Pe, but not ERN, associated with decreased awareness of deficits [177] - Error-related signals enhanced if participants are aware of false presses to incongruent/repeated Stroop stimuli [178]. - Anxiety and depression in TBI impairs performance-monitoring (181). Negative symptoms are inversely correlated with ERN amplitude i.e. emotional sequelae of TBI compromise monitoring efficiency. - Pharmacological studies Dopamine agonists enhance error monitoring ERPs [182] The property has potential for use by the pharmacology industry eg: new/ candidate medication for TBI restoring depleted dopamine may normalise ERN amplitude.

Table 1 Continue

Table 1. ERP markers of cognitive and social function in TBI subjects (Adapted and modified from Dockree *et al.* [195])

Response inhibition	- The right inferior frontal gyrus (IFG) and the subthalamic nucleus (STN) are key players in inhibition of responses and task-sets [183,184]. - Deactivation of the pars opercularis in the right IFG impairs the ability to disengage an initiated action however the ability to initiate an action is retained [185]. - Thalamocortical output suppression is seen in top-down control processes while bottom-up stimulus-driven go/no-go tasks use midline-lateral PFC [186-188]. Within healthy controls individuals who more self-rated cognitive failures rely on 'last-gasp' ACC engagement to inhibit a response while those reporting less-to-no cognitive failures had a pre-emptive 'slow-and-steady' right PFC pattern - Shearing of white matter connectivity (prefrontal, parietal and cerebella) following TBI may cause timing deficiencies that result in a switch from predictive to a reactive mode of engagement [189]. For example if optimal timing required for PFC to integrate sensory information then the frontal regions step in reactive mode. - Go/no-go tasks where participants must respond to every alternating stimulus but withhold to a repeated stimulus TBI subjects made more errors than controls and a speed/accuracy trade off was observed. TBI patients with faster RTs had more synchronized alpha power over mid-line fronto-central region indicating PFC down-regulation [190 8]. N2 and P 3 ERP components were reduced on no-go trials in TBI patients versus controls possibly due to loss of temporal efficiency that enable timely inhibitory control. - Emotional responses (generated by the orbitofrontal cortex-OFC) are also inhibited in TBI patients. TBI commonly affects the anterior PFC and the OFC; failure to suppress or gate emotional reactions due to impaired OFC function could cause socially inappropriate behavior [191-195]. Patients with orbital frontal lesions show enhanced P3 in response to somatosensory and auditory stimuli compared to healthy controls and individuals with dorsolateral prefrontal lesions. Habituation to stimuli was also lost in subjects with OFC lesions [192]. - Failure of evaluative and regulatory mechanisms (switching between different instructional task-sets during a cued Stroop colour-word task) may be the reason flexible deployment of attention in TBI subjects is impaired [125]. - TBI subjects were less able to efficiently detect colour-word conflict and under incongruent conditions did not produce a fronto-central N450 seen in controls and source-localized to the ACC [174]. - The centro-parietal conflict slow potential (conflict SP) elicited using incongruent Stroop trials is reduced in controls and not reduced in severe TBI subjects this could account for their lack of flexibility during conflict [193].
Word Retrieval and Language	- The N400, P600, Left Anterior Negativity (LAN) and Mismatch Negativity (MMN) are ERP components used in language research [196-201]. - When subjects evaluate word pairs that facilitate retrieval compared with responses elicited by word pairs that do not facilitate retrieval a 750msec ERP is elicited located at the left fronto-temporal region [197]. - A study investigated the neurophysiological correlates of word retrieval networks in 19 retired professional athletes with TBI and 19 healthy control (HC) subjects [197]. There were no significant differences in accuracy or RT between the two groups. The EEG showed a significant group by condition interaction over the left fronto-temporal region. The HC group mean amplitudes were significantly different between conditions, but the TBI group data did not show this difference, suggesting neurophysiological effects of injury.

Table 2. EEG studies on mTBI and conditions also exhibiting similar EEG patterns. Adapted and modified from Rapp *et al.* [45]. #Adapted and modified from Bonita *et al.* [231]

EEG Spectral Power [202-208]	Frequency range	mTBI and Spectral power		
		Decrease	Increase	Unchanged
	Delta	Tebano <i>et al.</i>	Korn <i>et al.</i>	
	Theta		Tomkins <i>et al.</i>	Tebano <i>et al.</i>
	Alpha	Korn <i>et al.</i> , Gosselin <i>et al.</i>	Tebano <i>et al.</i>	Chen <i>et al.</i> Tebano <i>et al.</i>
	Beta	Tebano <i>et al.</i>	Thornton	Tebano <i>et al.</i> Chen <i>et al.</i>
	Gamma			
	Theta/alpha	Chen <i>et al.</i>	Watson <i>et al.</i> , Chen <i>et al.</i>	
	Alpha1/alpha2		Chen <i>et al.</i>	
Synchronization of EEGs [158,190,209-216]	TBI studies altered synchronization of EEGs Dockree <i>et al.</i> 2004, Hoffman <i>et al.</i> 1995, Kumar <i>et al.</i> 2009a,b, Roche <i>et al.</i> 2004, Slewa-Younan <i>et al.</i> 2002, Thatcher <i>et al.</i> 1999, 2000, 2001, 2006 Neuropsychiatric disorders that also exhibit altered synchronization of EEGs AD/HD, Alcohol abuse, Alexithymia, Autism, Bipolar disorders, Dementia, Depression, Hallucinations, HIV dementia, Migraine, Multiple sclerosis, Neuropsychiatric disorders: general reviews, Parkinson's disease, Post-traumatic stress disorder, Schizophrenia and other psychotic disorders			
Functional connectivity # [204,211,212,217-226]	mTBI and Altered functional connectivity Cao and Slobounov 2010, Kumar <i>et al.</i> 2009a,b, Castellanos <i>et al.</i> 2010, 2011a,b Nakamura <i>et al.</i> 2009, Ham and Sharp 2012, Sponheim <i>et al.</i> 2011, Kasahara <i>et al.</i> 2010, Tsirka <i>et al.</i> 2011, Thatcher <i>et al.</i> 1991, Thornton 2003 Pathological conditions also associated with altered functional connectivity Alzheimer's disease, Epileptic seizures, Intra-arterial amobarbital injection, Autism spectrum disorder, Brain tumors, Multiple sclerosis, Preterm birth, Post traumatic stress disorder (PTSD), Schizophrenia, Stroke.			
Network Geometries [217-221,225,227-230]	TBI studies showing altered network geometries: Cao and Slobounov, 2010, Castellanos <i>et al.</i> , 2010, 2011a,b, Nakamura <i>et al.</i> , 2009, Tsirka <i>et al.</i> , 2011, Zouridakis <i>et al.</i> , 2011, Irimia <i>et al.</i> , 2013a, b, Goh <i>et al.</i> 2014, Neuropsychiatric disorders also exhibiting altered network geometries Alzheimer's disease, CNS tumor, Depression, Epilepsy, Schizophrenia			

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