Journal of Systems and Integrative Neuroscience

Review Article ISSN: 2059-9781

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 oribitofrontal 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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Received: March 11, 2020; **Accepted:** April 06, 2020; **Published:** April 10, 2020

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 (F_0) 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; TTLL7; ADAMTS9; ARHGAP20; CAMK4; ELMO1; LIPC; PDE7B; PLEKHG1; SP6*
ADHD	*BCL11A; CDH13; LRRC7; LYPLAL1; NR4A2; SEMA3A; TCEB1; TGFB2; TSHZ2; ZIC5; PAWR; NDN, ESRRB; ADAMTS2; LRRN3; TYRP1*
Bipolar disorder	*ANK3; COLEC12; DGKH; DPP10; IRF2BP2; ITIH3; MRPS23; MSI2; NFIA; PDE10A; PGM5; PPM1M; SIAE; SP8; TTC39B; UACA; CGNL1; DMTF1; FAT4*
Bipolar disorder and schizophrenia	*ARC; ATP6V1B2; BAI1; CACNA2D1; CMYA5; COMMD10; CST7; CTNND2; DDX52; DMD; HACE1; IRX1; KAT2B; MRVI1; MYO1E; PRKCQ; PTPRN2; SIM1; SLC39A12; TMEM212; TTC39B; VPS13C*
Brain connectivity	*CNTN4; EPHA7; NEDD4*
Brain structure	*BOK; CADPS2; GRIN2B*
Cognitive function	*PTPRO; AFAP1L2; CDH13; FAT4; GABRQ; GRIN2B; HCCS; IMMP2L; IRX1; IRX2; JUN; KIAA1217; KLHL1; LHX2; LIPC; MCTP2; NR2F2; PLCB1; RIT2; TOX; TSHZ3; UNC13C; VANGL2; ZNF788; LMO4*
Word reading	*NOS1AP; TACSTD2; TYRP1*
Working memory	*CLDN1; DRD2; LPHN3*
Conduct disorder	*C1QTNF7; MCTP2; NR2F2; RIT2; ST8SIA4; ZBTB16; KCNA5; PDE10A*
Eating disorders	*CAMK1D; DLGAP1*
Hippocampal atrophy/volume	*APOE; COL18A1; F5; MAGI2; MAL2; DPP4; MSRB3*
Intelligence	*CNTN4; COL1A2; GYPC; KIF16B*
Major depressive disorder	*ADCYAP1R1; CCND2; CDH9; EMP1; GRIN2B; HAPLN1; HOMER1; IGFBP3; KCNH5; NDFIP2; NEUROD6; PCLO; RASGEF1B; ATP6V1B2*
Parkinson's disease	*BMP4; DLG2; GPRIN3; RIT2; RORA; SEMA5A; STK39; VPS13C; WNT3*
PTSD	*COBL; PCSK2; PRKCA; SLC4A5*
Schizophrenia	*ANK3; 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

Masterson, Caitlin, (2019).Theses, Figure 3.3, Page-26

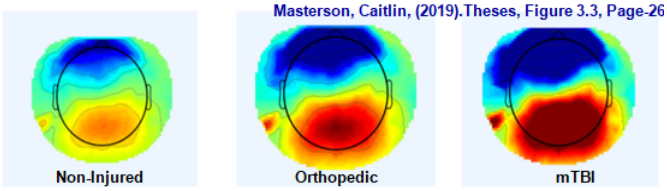

Figure 1. Factoring in Homology and the other-injury factor when looking for markers of TBI- and neurocognition [46,47]

Gaetz & Bernstein, 2001 (51)

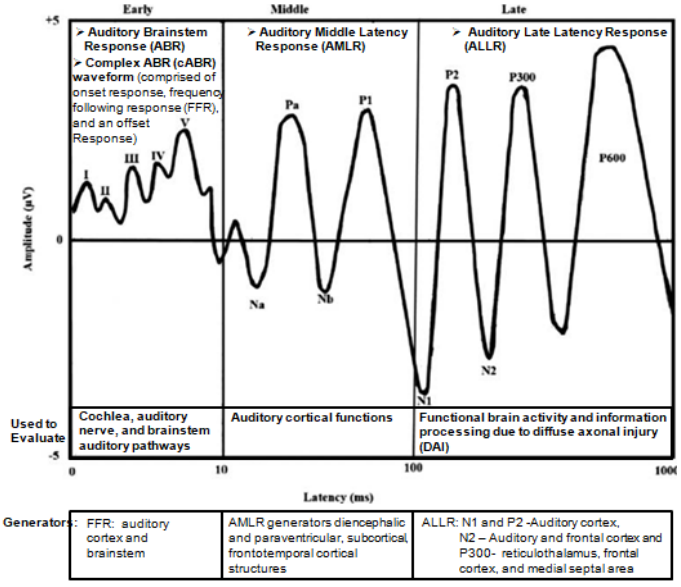

Figure 2. Auditory evoked potentials (AEPs)

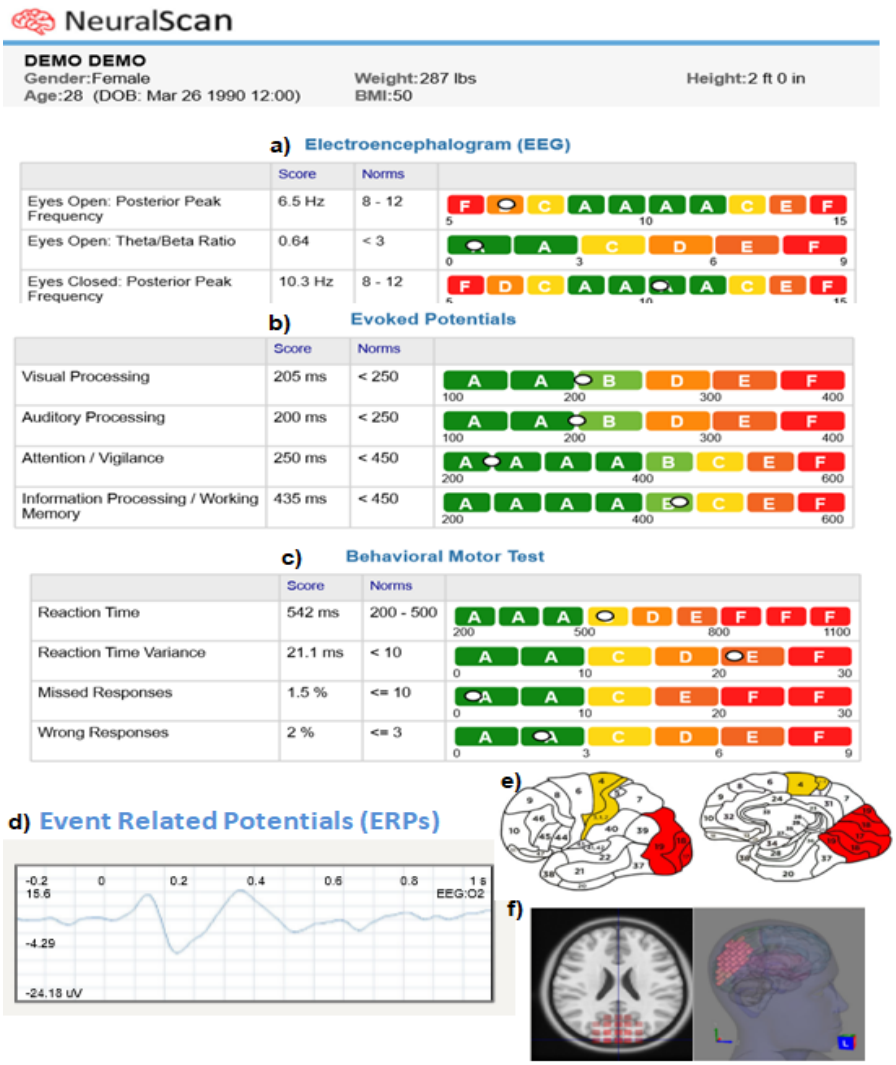

Figure 3. Illustration of AEPs, VEPs, and cognitive function captured using NeuralScan by Medeia.

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 Broadmann 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 ≈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 (llVEP) remained within normal patterns. The inference was that tsVEP elicited after llVEP (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 persistant 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

a) inherent overlap and homology between TBI and its psychiatric, neurological and neuropsychiatric post-TBI sequelae,

b) 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.

c) 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. • Pharmacolo**gical 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 *et al.*	Korn *et al.*	
	Theta		Tomkins *et al.*	Tebano *et al.*
	Alpha	Korn *et al*., Gosselin *et al*.	Tebano *et al.*	Chen *et al.* Tebano *et al.*
	Beta	Tebano *et al.*	Thornton	Tebano *et al.* Chen *et al.*
	Gamma			
	Theta/alpha	Chen *et al.*	Watson *et al.*, Chen *et al.*	
	Alpha1/alpha2		Chen *et al.*	
Synchronization of EEGs [158,190,209-216]	**TBI studies altered synchronization of EEGs** Dockree *et al.* 2004, Hoffman *et al*. 1995, Kumar *et al.* 2009a,b, Roche *et al.* 2004, Slewa-Younan *et al.* 2002, Thatcher *et al.* 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 *et al.* 2009a,b, Castellanos *et al.* 2010, 2011a,b Nakamura *et al.* 2009, Ham and Sharp 2012, Sponheim *et al*. 2011 , Kasahara *et al*. 2010, Tsirka *et al.* 2011, Thatcher et al 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 *et al.,* 2010, 2011a,b, Nakamura *et al.,* 2009, Tsirka *et al.,* 2011, Zourdakis *et al.,* 2011, Irimia *et al.,* 2013a, b, Goh *et al.* 2014, **Neuropsychiatric disorders also exhibiting altered network geometries** Alzheimer's disease, CNS tumor, Depression, Epilepsy, Schizophrenia			

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Journal of Systems and Integrative Neuroscience

Research Article ISSN: 2059-9781

Electroencephalography (EEG)-based detection, management, recovery and brain retraining tracking of Traumatic Brain Injury (TBI) when "*Only Time Can Tell*"

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Abstract

Traumatic brain injury (TBI) can be caused by accidents like road traffic accidents (RTA), sports injuries, and injuries at home. It is a major health issue, very often fatal and causing high morbidity, changing the lives of both the person injured and the families involved. Anticipating and preventing secondary injury and seizures post-trauma, defining severity of TBI, predicting TBI outcomes and arousal from coma or declaration of vegetative state or brain death form pivotal checkpoints in TBI management. Other challenges faced include identifying malingerers from genuine individuals with post-TBI morbidity, defining the severity of previous TBI in the field or previous injuries when reports are lost. Depending on both its severity and location it can cause a variety of post-TBI cognitive, sensory and tactile, and motor impairments. In such instances the present paper looks at how the electroencephalographs (EEG) like NeuralScan can and do contribute uniquely and significantly aiding in assessment, continuous/periodic evaluation during the course of recovery, brain-retraining and rehabilitation in evaluating temporal changes in neuronal functionality following TBI.

Vital statistics on traumatic brain injury (TBI)

To better appreciate the unique and valuable contributions that the high temporal resolution electroencephalograph (EEG) like NeuraScan provide in the detection, classification, treatment, management and rehabilitation of traumatic brain injury (TBI) a brief review of the key epidemiology, consequences, co-morbidities, neuropathophysiology and outcomes of TBI is appropriate. In 2016, the incidence of traumatic brain injury (TBI) was 27·08 million and prevalence was 55·50 million [1]. In 2018 the global incidence of TBI was 69 million individuals worldwide and predicted to be the third leading cause of mortality in 2020 [2-5]. Incidence rates based on TBI severity determined using 6 studies are that mild TBI affects approximately 55.9 million people each year (740 cases per 100,000 people), moderate TBI affects 7.64 million people each year (101 cases per 100,000 people), and severe TBI affects 5.48 million people each year (73 cases per 100,000 people) with the proportion of mild, moderate and severe being 81.02%, 11.04%, and severe 7.95% respectively [5-10]. The causes of traumatic brain injury (TBI) range from falls, motor vehicle accidents (traffic and pedestrian), self-harm (falls, gunshot wounds-GSW), abuse/domestic (adult or children) violence, street violence, work/industrial/construction incidents (falls, blasts) and military maneuvers/terrorism, (falls, fire arms, blasts, explosions).

Following a TBI the duration from injury to recovery (Figure 1: LORETA images tracking injury to recovery taken using NeuralScan by Medeia) can vary depending on the duration between injury and commencement of treatment, severity and location of the injury. While earlier it was thought that only moderate-severe TBI survivors (50-65%) experience debilitating emotional, psychological and neurocognitive consequences (Figures 2a and 2b) in recent year's studies have shown that individuals (athletes, military personnel and elderly) with mild TBI (mTBI) also share the same risk [4-7,11-16]. mTBI accounts for 1.6-3.8 million sports-related 320,000 military-related concussions [17-20]. The consequences of TBI affect personal, social and work life as well as influence the rate of age-related cognitive decline [20-29]. Military veterans with mTBI have been shown to be at a 56% increased risk of Parkinson disease (PD) [30]. Studies on TBI and the risk of dementia or Alzheimer's disease (AD) have shown no similar association [31].

Whether it's mild or, moderate or severe TBI though for some individuals return-to-normal it is uneventful for many others it requires a concerted and integrated approach on the part of a myriad medical specialties extending to family, social and occupational support where rehabilitation is concerned [32-38] an individual. *Further compounding the issue is that many individuals with possible/probable mild TBI following sports injury, falls and road traffic accidents (RTA) etc do not seek treatment.* A survey of 1381 individuals with TBI found 42% did not seek treatment with age, severity of TBI and injury occurring at home being factors associated with not seeking treatment [32,39]. Similarly, less than half of patients (41% [343 patients]) reported having seen a medical practitioner about their mTBI at 2 weeks, and 44% (367 patients) reported seeing a medical practitioner by 3 months [40-42]. Another feature of mTBI is that very often individuals do not seek medical care, among those who do seek care there is a lack of follow-up care even if they tested positive on computed tomography (CT)

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Received: May 28, 2020; **Accepted:** June 19, 2020; **Published:** June 21, 2020

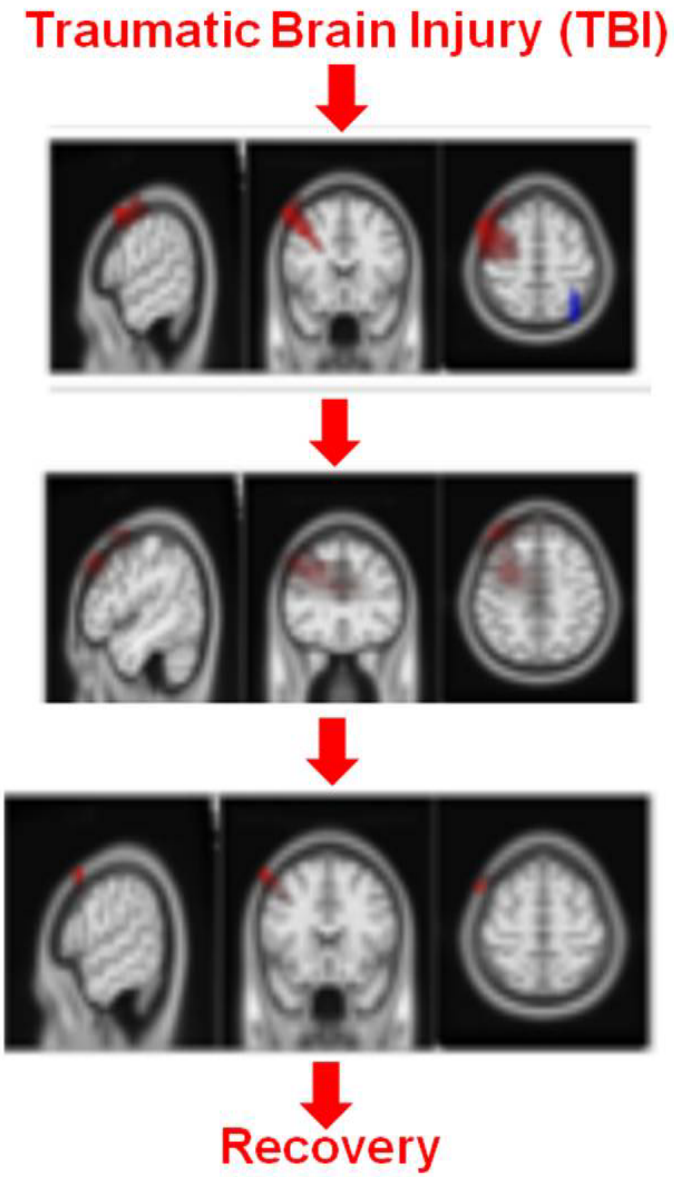

Figure 1. Working example of the dual use of eLORETA/sLORETA: To "track TBI" from injury to recovery, To "track Z-score retraining of the brain", LORETA Images taken using NeuralScan by Medeia

and post mTBi symptoms exist/persist symptoms this in turn results in longer-lasting symptoms which may have long-term consequences [40-42].

Another key aspect about TBI is it is dynamic. A brief overview of the neuropathology of TBI is presented in Figure 3 which illustrates how both the primary and secondary injuries influence outcomes [43-45]. Figure 3a presents the different types of primary injury that can occur, the consequences of which is the secondary injury (Figure 3b) which can happen within minutes or days following the trauma. The secondary injury is the result of the cascade of events (molecular, chemical, and inflammatory) that are activated following the primary injury [43-45]. Hence one of the main goals of TBI treatment protocols is to repair the primary injury and prevent secondary injury which if left unchecked can cause further cerebral damage [43-45].

Short and long term outcomes of traumatic brain injury (TBI) vary depending on the severity of injury (primary and secondary), co-morbidities during hospitalization and following discharge, location of the injury, medical history prior to the TBI, previous TBI, presence of polytrauma [16,32-38,46-48]. At 8-years following a TBI, 19.8% and 46.5% were severely and moderately disabled respectively with 33.7% with good recovery among 86 individuals who participated in the study. Somatic complaints were balance 47.5%, motricity 31%, and headaches 36%, cognitive complaints: memory 71%, slowness 68%, concentration 67%, 25 % had anxiety and 23.7% for depression. 48.7% were employed in a productive job and 38% declared a salary loss since the TBI [46].

When only time can tell

Among the several studies aimed at determining blood, imaging and electrophysiology (EEG) based markers to classify, monitor and

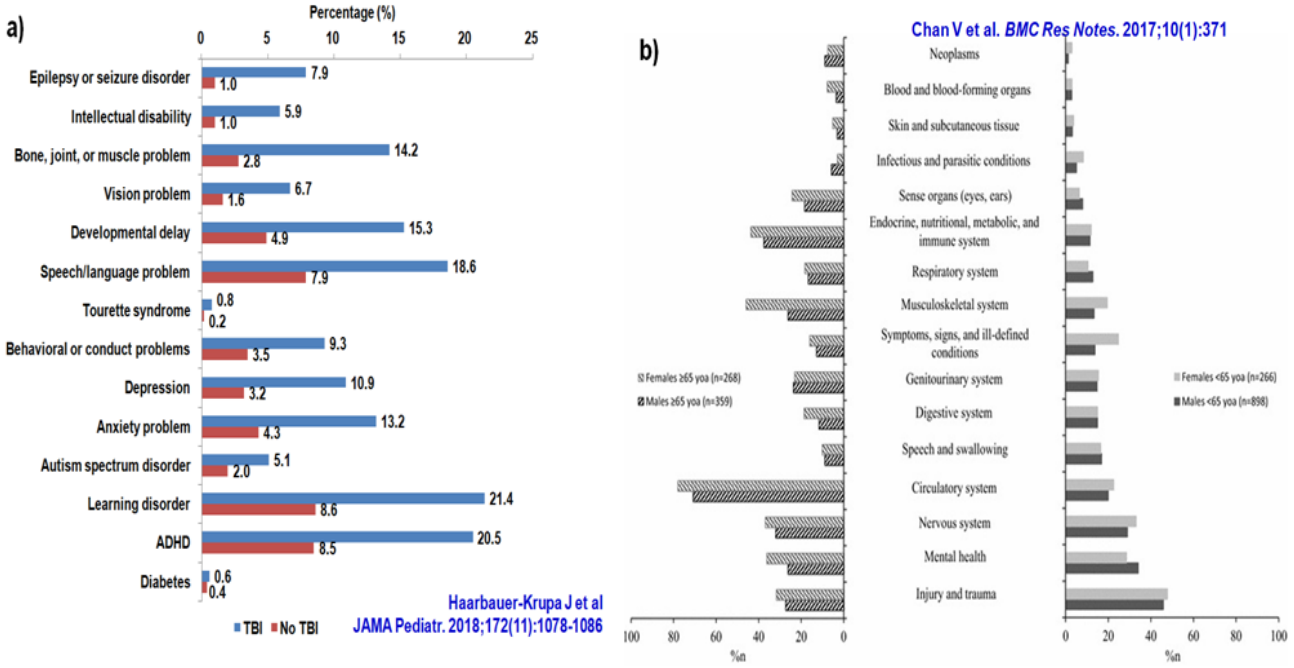

Figure 2. Prevalence of co-morbid conditions among a) Children (parent-reported), and b) <65 and ≥65 year-old Adults following TBI

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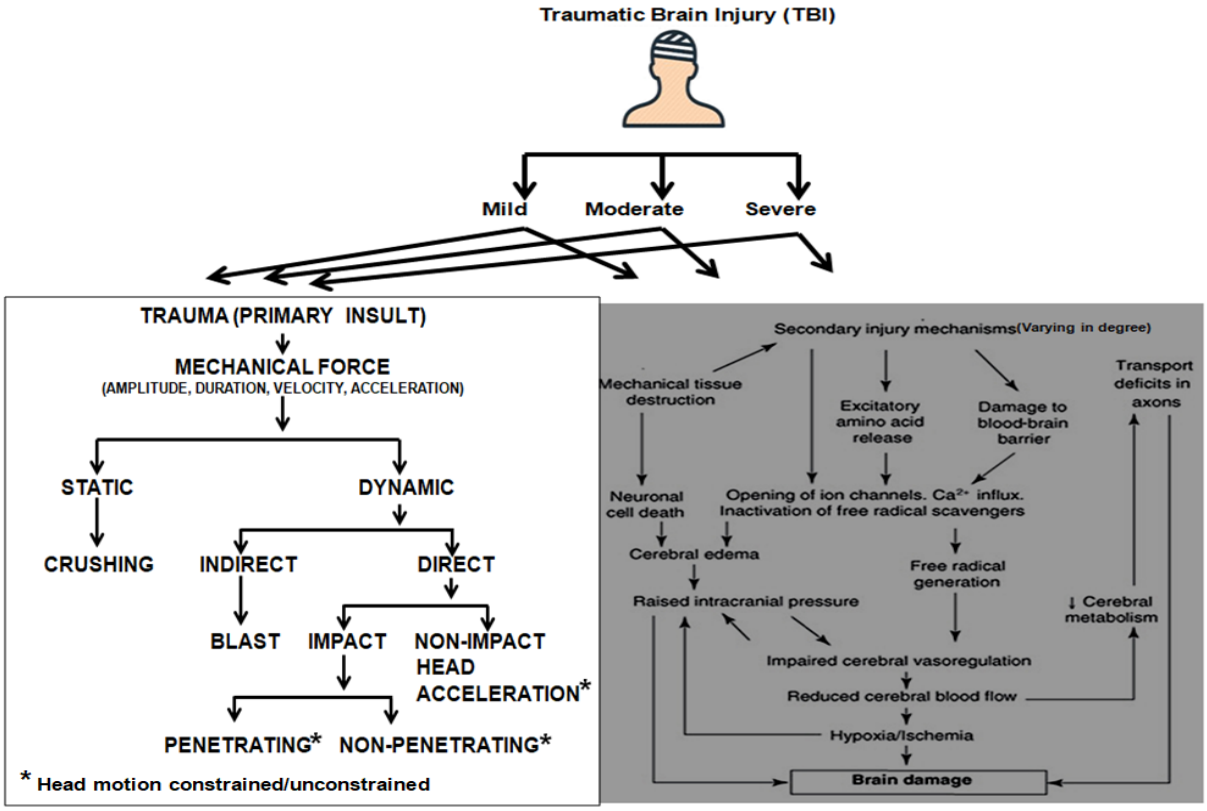

Figure 3. Trauma brain injury and its neuropathophysiology

treat TBI the EEG (machines like NeuralScan by Medeia) remains one of the earliest neurodiagnostic assessment tools that was used [49,50]. Denis Williams recommended and demonstrated the use of the EEG both in evaluating progress in cerebral repair and when the damage is so slight that it cannot be detected by other imaging techniques [50]. He advocated the EEG as a useful tool when monitoring the brain following initial trauma, monitoring to prevent secondary injury and when planning treatment and rehabilitation (Figures 4a and 4b). Following a TBI there are several time points (as mentioned below) at which the high temporal resolution, quantitative EEG (QEEG) and LORETA for spatial resolution that EEG machines like NeuralScan by Medeia offer is key (Figures 1, 4a, 4b and 5) .

Identification, Monitoring and treatment of Seizures following TBI: The portable non-invasive EEG allows for evaluating a patients electrophysiological status at the trauma site or bedside (emergency room/ trauma unit/operation theatre/intensive care unit-ICU) enabling identification of nonconvulsive seizures (NCS) following cerebral, trauma monitoring of treatment and categorization of the severity of the TBI [51-56]. NCS and periodic discharges (PD) following TBI contribute to disruption of brain metabolism [51-56]. Of the 94 patients with moderate-to-severe TBI seizures occurred in more than one in five patients during the 1st week following primary injury [51]. As NCS are found to occur frequently following a TBI and require continuous EEG (cEEG) monitoring for timely detection, prevention or treatment of NCS

a

EEG Parameters	QEEG Z -Scores	LORETA 8 Functional Networks	Brain Cortex- Brodmann Areas- Functional regions: Brodmann Areas	Total Brodmann Pairs	Brain Cortical Regions
• Brain waves • Evoked potentials • ERPs • Sleep Studies • Resting EEG (Eyes Open & Eyes Closed) ➢ *Amplitude,* ➢ *Power,* ➢ *Frequency,* ➢ *Latency*	• 8-Functional Network ➢ *Amplitude asymmetry* ➢ *Coherence* ➢ *Absolute phase* ➢ *Instantaneous connectivity* ➢ *Lagged connectivity*	Anxiety	4,6,7,10,13,21, Amygdala	42	• Frontal lobe • Parietal lobe • Occipital lobe • Temporal lobe • Posterior Cingulate, • Anterior Cingulate gyrus, • Parahippocampal gyrus
		Attention Dorsal	6,7,8,19,39,40	30	
		Attention Ventral	10,11,19,21,37,44,45	42	
		Default Mode	7,10,11,19,22,29,30,31 ,35,39,40	110	
		Language	22,39,40,41,42,44,45 Left Hemisphere only	21	
		Memory	7,9,24,30,31,32,33,40, Hippocampus	72	
		Mood	10,11,13,23,24,32,33,4 4,45,47	90	
		Pain	1,2,3,4,5,13,24,32,33	72	

RW Thatcher (1989, 1991, 2001, 2010), J. Zhang 2019

Brain waves: *Delta, Theta; Alpha1; Alpha2; Beta1; Beta2; Beta3 and High Beta or Gamma*
Evoked potentials: *(Visual evoked potential-VEP, Auditory evoked potential-AEP, Somatosensory evoked potential-SSEP, Motor evoked potentials-MEP, and Steady-state evoked potential-SSEP),*
Time-locked EEG activity/Event-related Potentials (ERPs): *Early left anterior negativity-ELAN, Error-related negativity-ERN, Late positive component-LPC, Lateralized readiness potential-LRP, Mismatch negativity-MMN, N100 (Visual N1 and Auditory N100), N170, N2pc, N200, N400, P3a, P3b, P200, P300 (neuroscience), P600*
Brain Cortical regions and their Function: *Frontal lobe (thinking, planning, motor execution, executive function, mood control), Frontal lobe (thinking, planning, motor execution, executive function, mood control), Parietal lobe (Somatosensory-vision and somatospatial: information integration), Occipital lobe (visual perception and processing), Temporal lobe (language, auditory, long-term memory and emotion, Posterior cingulate gyrus (attention, long-term memory), Anterior cingulate gyrus (volitional movement, attention, long-term memory), and Parahippocampal gyrus (short-term memory, attention)*

b

After I was released from the hospital (a week and a day after the fall) my physiatrist followed up regularly during the first month and adjusted exercises as needed. I had absence seizures and was on anticonvulsant medications until I was around 21 years old. ***I had regular blood work, electroencephalograms (EEGs), and follow-ups with neurologists and neurosurgeons to make sure everything was under control.*** *The other sequela that lingered was short-term memory impairment. I continued to work on fine motor control for some time; after several months, I was playing the recorder and the flute again and even rejoined the orchestra.*

Figure 4. (a) Current and potential EEG-based markers for both "TRACKING RECOVERY and brain RETRAINING". (b) Excerpts from a Case Study illustrating both the use of EEG in TBI treatment and what is possible when high-quality acute and post-acute care are provided, even after 5-hours delay in the identification of TBI. Taken from: Panel 6 "a patient's testimony"; Maas AIR et al, Lancet Neurol. 2017 [38]. In 1988, 12 year old, Laura E Gonzalez-Lara fell down an orchestra pit as she took part in a concert in a small town in Mexico and suffered a TBI. TBI identification and treatment commenced ***5-hours after her injury.*** Gonzalez-Lara benefited from the support of her parents, both physicians, and extended family

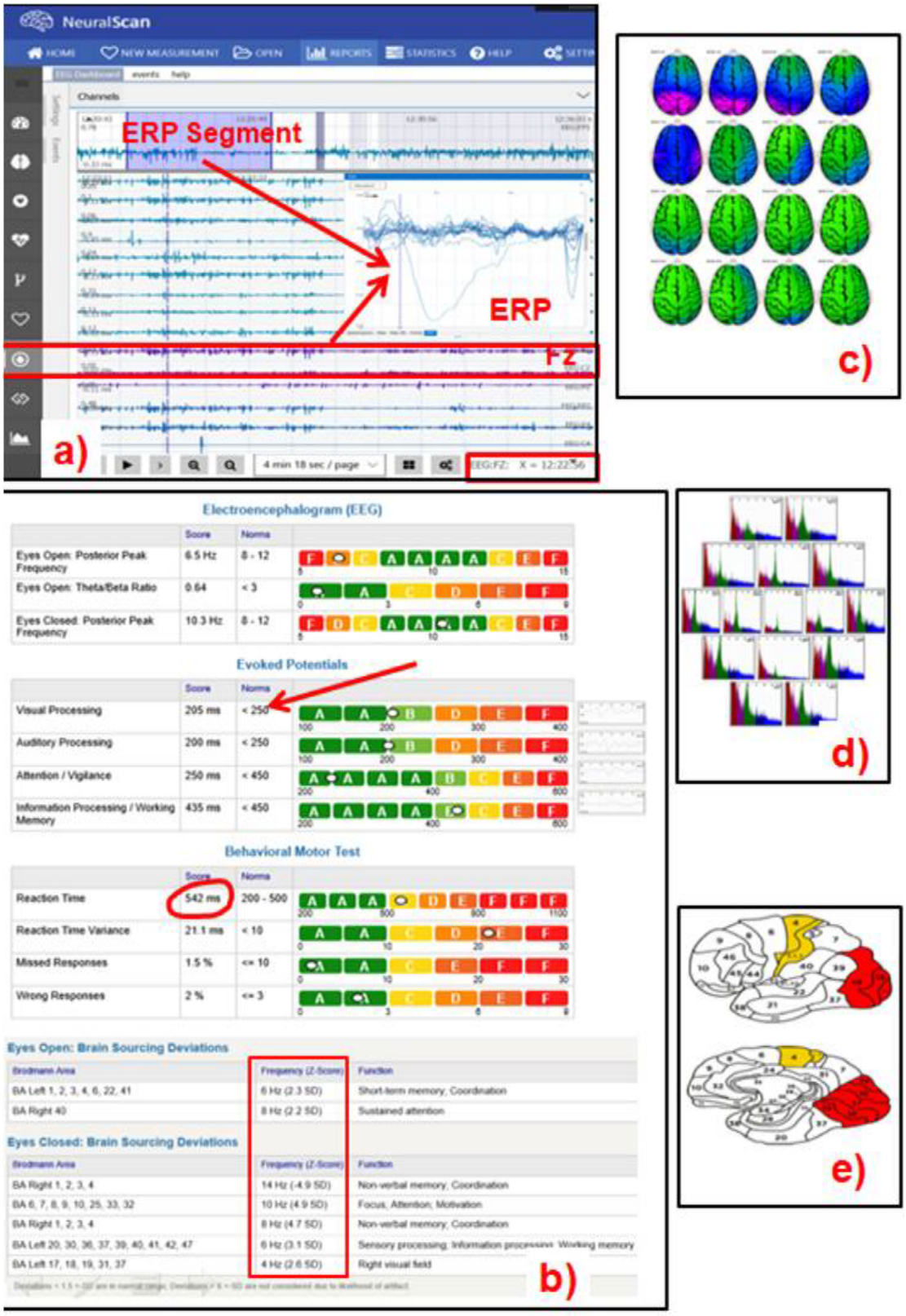

Figure 5. The potential of NeuralScan by Medeia in "TRACKING RECOVERY and brain RETRAINING" (Images of both features and reports that NeuralScan comes with; a)19-channel EEG tracing capturing ability, EEG tracing at rest, evoked potentials and event related potentials (ERP, b)Reports on visual and auditory processing, attention, working memory, reaction-time (RT), RT variance (RTV), missed and wrong responses, assessment of Broadmann areas in terms of their function ability, c) qEEG and topographical maps, d)time frequency analysis and e) identification of Broadmann areas affected)

[51-56]. In a prospective multicenter study of severe TBI (n=34) surface and invasive intracortical depth electroencephalography (EEG) was carried out [54]. Cerebral microdialysis was carried out simultaneously to measure lactate/pyruvate ratio a marker of metabolic crisis. NCSs or PDs occurred in 61%. 42.9% of the NCSs were only captured when intracortical depth EEG was used. The maximum duration of NCS was many hours. Disruption of cerebral metabolism was seen during NCS or PDs but not during electrically nonepileptic epochs [53]. NCS following TBI has also been correlated with hippocampal atrophy [55].

EEG- based markers to classify TBI severity

To classify the severity of TBI three parameters are required, the Glasgow Coma Score (GCS), duration of loss of consciousness (LOC) and duration of posttraumatic amnesia (PTA) [57-59]. However each parameter has its own technical difficulties ranging from the subjectivity and inter-rater variability of the GCS to patient being unaware of the exact time when consciousness or memory was lost and at times the GCS or LOC or PTA or all three were not obtained [58-60]. To make the classification of TBI severity more objective an EEG-based index of TBI severity was developed. The EEG's ability to identify blast concussions years later, in outpatients, mild TBI (following injury accuracy 95.67% with >75.8% accuracy 1-year after the injury) have been demonstrated [61-65].

In 1989 Thatcher demonstrated the EEGs ability to discriminated between mild TBI in a study of 608 mild TBI and 108 age-matched normal subjects (overall discriminant classification accuracy=94.8%) and cross-validated the findings in three separate independent study populations [63,64]. The EEG features associated with mechanical head injury were: "i)increased coherence and decreased phase in frontal and frontal-temporal regions; ii)decreased power differences between anterior and posterior cortical regions; and iii)reduced alpha power in posterior cortical regions" [65]. In a QEEG study of 91 subjects (32 mTBI with <20 minutes LOC, 9 TBi with > 20 minutes LOC and 52 normal individuals) 1999 Thornton evaluated the robustness of these EEG variables at >1-year following TBI [66]. The high frequency discriminant developed by Thatcher classified the severity of 100% of TBI subjects at 1-year post-TBI, 87% of subjects at all time periods and 79% of subjects 43-years post injury. To derive the EEG index of TBI severity, 108 patients with closed TBI 15 days to 4 years after injury (mild TBI n=40, mild TBI n=25, and severe TBI n=43) were studied via eyes-closed resting EEG and power spectral analyses of 2- to 5-minute segments was done (19 electrodes, International 10/20 System, left ear lobe as reference). Discriminatory ability of the index of severity index developed from the EEG variables was between mild versus (vs) severe TBI groups was accuracy=96.39%, sensitivity=95.45%, and specificity=97.44% and the t-test showed significant difference between groups (Mild vs. Moderate, p<0.0001; Mild vs. Severe, p<0.000001; Moderate vs. Severe, p<0.00001) [65].

Naunheim and Neil took these findings further for two reasons; i) the incidence of TBI and mild TBI making computed tomography (CT) imaging in acute mTBI expensive and impractical, ii)70% of individuals with TBI selected for CT using criteria like the New Orleans Criteria (NOC) were CT negative [67,68]. Naunheim validated the qEEG TBI severity index (specificity 90%) in 105 TBI subjects (53 CT positive - TBI discriminant index of 80.4 and 52 CT negative-TBI discriminant index of 38.9) and 50 healthy controls (TBI discriminant index of 24.5) [67]. Neil studied 119 patients with mTBI, the patients were screened using a) CT and b) qEEG, using the EEG-based index of TBI severity (0 minutes, eyes closed resting EEG with frontal electrodes FP1, FP2, AFz, F7, and F8, referenced to linked ears arranged according to the International 10/20 system) to determine if they required a CT or not. Using Marshall's criteria the subjects were then classified as CT positive or negative. TBI-Index and the NOC had sensitivities, at 94.7% and 92.1% respectively [68]. The specificity of the TBI-Index versus NOC was 49.4% versus 23.5%, positive predictive value, negative predictive value and positive likelihood ratio were better with the TBI-Index, combining both indices increased sensitivity to obtain a positive CT result to 97%. [68].

Predicting TBI outcomes and readiness to-return-to-play/work/drive: In patients with moderate or severe TBI it can be used to guide assessment and treatment post-TBI (primary injury), for early identification of secondary injury if any, in recovery, prior to discharge and rehabilitation (Figure 3) in particular if neurocognitive therapy is required and in determining if the patient is ready to-return-to-play/work/drive. Invasive continuous EEG (cEEG) is used in monitoring secondary brain injury [38].

Predicting TBI outcomes: Assessment of consciousness level is important in patients with TBI as it aids clinicians in treatment decision making. The bispectral index (BIS, ranging from 0: isoelectric signals to 100: conscious patients) originally used to measure the clinical state of anesthesia was evaluated in a study by Senapathi as a candidate marker of consciousness and sedation level in TBI patients (n=78) with decreased consciousness. BIS value was highly correlated with GCS score (r=0.744, p< 0.01) in TBI patients [69]. Mean BIS values of mild, moderate, and severe head injury were 88.1±5.6, 72.1±11.1, and 60.4±11.7, respectively. Further an equation to predict GCS from a BIS value derived using linear regression analysis: GCS = 0.21(BIS) – 5.208. Mahadewa assessed the correlation between Glasgow Outcome Scale-Extended (GOS-E) scores calculated 6 months after the TBI event with BIS values on admission in 68 TBI patients who underwent craniotomy, correlation was at r =0.921, p<0.01 (70). Findings suggest that BIS scores upon admission may be used to predict the outcomes in patients with TBI. An equation to predict GOS-E from BIS value derived from the linear regression analysis in this study, and this is GOS-E =0.19(BIS) – 8.3 [70].

EEG features of worse outcome following a TBI include lower (regional) EEG power, slowing of the EEG decrease in alpha power, lower EEG (alpha) variability, and increased coherence [50,63,71-78]. A recent study by Haveman used multifactorial Random Forest models and qEEG parameters to predict outcome in 57 patients (training set; n = 38 and a validation set; n = 19) with moderate to severe TBI [78]. Outcome at 12 months by the Extended Glasgow Outcome Score (GOSE) was categorized as poor (GOSE 1–2) or good (GOSE 3–8). Twenty-three qEEG features were extracted to develop the multifactorial Random Forest model which was compared with the International Mission for Prognosis and Clinical Trial Design (IMPACT) predictor in its ability to predict outcomes via GOSE. The predictive ability of the new model was evaluated using leave-one-out (area under the receiver operating characteristic curve-AUC for the training set was AUC= 0.94, (specificity 100%, sensitivity 75%) and validation set AUC = 0.81, (specificity 75%, sensitivity 100%). The IMPACT predictor had an AUC of 0.74 (specificity 81%, sensitivity 65%) and 0.84 (sensitivity 88%, specificity 73%), respectively.

Monitoring cortical spreading depolarizations: Another feature occurring following a TBI and warranting monitoring is cortical spreading depolarizations which are associated with worse prognosis. The neuropathophysiology behind this feature is that cortical spreading

depressions, or propagating waves of astrocyte depolarization have been linked with the neuropathological cascade that characterizes secondary injury [43-45,56-63].

Determining readiness to-return-to-play/work/drive: In the interest of brevity we will briefly discuss EEGs potential to determine readiness to-return-to-play/work/drive using sports-related-injury as a classic example. Following mTBI symptoms and in the clinical recovery stage of moderate and severe TBI while symptoms resolve it is imperative that the brain is allowed sufficient time to heal. Athletes/coaches/military personnel tend to underreport symptoms due to personal goals, pressure and desire not to let down teammates. Sustaining multiple concussions before the brain has had time to heal has revealed an excess of amyloid-beta plaques and tau tangles in autopsies of football players, possibility of chronic traumatic encephalopathy (CTE) dementia, mental health issues, and depression [79]. A brain recovery can extend beyond the clinical recovery time, so an improved neurological function index is needed [79-82]. Post-TBI symptoms can last from 1-month to 3-months,and can even become chronic (even in mTBI-15%) when microstructure white matter lesions are present and fail to heal [83-86].

McCrea studied the clinical utility of the EEG from injury to recovery (eg: Figures 1 and 5) in a prospective, non-randomized study of 396 high school and college football players, including a subset of 28 athletes with concussion and 28 matched controls. Baseline measures of postconcussive symptoms, postural stability, cognitive functioning, and qEEG (preseason) were obtained [87]. On injury, qEEG, neurocognitive tests and symptom recording were carried out on day-Injury, day-8 and day-45 in the injured and control group. Results for the injured group were: *day-injury:* symptoms present till day-3, neurocognitive testing: results were poor and qEEG: showed abnormalities. *Day-8:* symptoms resolved, neurocognitive testing: return to baseline and qEEG: showed abnormalities. *Day-45:* symptoms resolved, neurocognitive testing: return to baseline and qEEG: return to baseline [87]. Another study by Barr on 59 athletes with TBI and 31 controls using qEEG to track injury and recovery on day-injury, day-8 and day-45 also yielded similar results [88]. The findings indicated that EEG abnormalities persist past clinical recovery and symptom resolution and are suggestive that return-to-play decisions are based on EEG patterns returning to baseline [89,90].

To increase the objectivity of the return-to or remove-from play decision and keeping the above findings in mind McNerney developed a scoring system combining both EEG and symptom questionnaires [91]. 38 individuals with mTBI and 47 controls were administered a symptom questionnaire, behavioral tests, and resting state EEG was measured [91-95]. 12 EEG variables were recorded (delta, theta, alpha, beta, sigma, and gamma bands from the A7-FpZ and A8-FpZ voltages). Accuracy was 75–82% when only symptoms were used to predict return-to-play, while EEG in combination with three-symptoms had an accuracy of 91%.

Assessment of coma, clinical recovery of consciousness and cognitive function: In patients presenting either at trauma site or at the ED who are unconscious/ in a coma and therefore assessment using verbal commands is futile triaging can classification of severity of TBI can be achieved and the depth of coma assessed using EEG. In comatose patients in a vegetative state it can be used in decision making regarding when life saving measures are futile. Three EEG features have been considered as prognostic indicators of recovery of consciousness, they include sleep spindles (hallmark of stage-2 sleep, absent in coma) (96,97), EEG reactivity (EEG-R, the EEG response to external stimulation) and EEG-awakening (a combination of EEG-R and sleep spindles). 106 individuals in a coma for >3 days were followed for 1 month, receiving operator curve (ROC) analysis revealed EEG-awakening (0.839; 0.757–0.921) to be the best prognostic indicator of recovery from consciousness followed by EEG-R (0.798; 0.710–0.886), sleep spindles (0.772; 0.680–0.864), and Glasgow Coma Score (GCS) scores (0.720; 0.623–0.818). ERPs involved in predicting awakening N100, mismatch negativity (MMN), and P300, is a highly significant predictor for awakening [96-99]. The absence of the somatosensory-evoked potential (SSEP) N2 in comatose patients has traditionally been regarded as a good indicator for the likelihood of non-awakening [100]. However, its presence does not guarantee recovery of consciousness [101,102].

Declaration of brain death: It can and is used in deciding if a patient is brain dead particularly in instances where organ donation is being considered by the next of kin.

Since brain death (BD) was first defined as "coma dépassé" there have been several efforts to reach a global consensus on best practices to be followed when declaring BD especially in view of organ transplantation [103-107]. Neurosurgeons and neurologists when surveyed about the standard best and objective BD declaration practices they followed 65% mentioned they required an isoelectric EEG; 29% needed only one EEG while 36% required two EEGs, 24 hours apart [108]. In order to increase the objectivity of BD declaration each test used has specific guidelines. EEG guidelines recommend use of a 16 channel, 10-20 system, 30 minute EEG recording, with auditory and bilateral somatosensory stimuli (touch and pain) repeatedly performed and clearly marked10,12 on the recording, with the time interval between the two EEGs dictated by age of the patient [109,110].

Metal shrapnel: In gunshot wounds (GSW) and blasts where metal shrapnel prevents assessment via neuroimaging (MRI and CT). In TBI caused by blasts and GSW the primary injury suffered by the individual is composed of injury due to the event, further injury by penetrating metallic shrapnel, the velocity with which the bullet is fired or the individual is thrown due to the blast and the injury caused as the individual falls (height of the fall and the surface texture on which the individual lands) [111,112]. Evaluating the severity of the injury using magnetic resonance imaging (MRI) warrants caution as the powerful magnet may cause further injury. In such instances EEG to assess TBI severity and TBI location via LORETA appears beneficial [111,112].

Malingering: Healthcare personnel and insurance companies use the EEG to ascertain if symptoms/complaints reported are due to current or previous TBI or other neurocognitive or neuorodegenerative disorders or malingering.

"Malingerers are individuals in who symptoms are consciously produced (either exaggerated or fabricated) to achieve their internal eg: achieving the sick role, when being evaluated for disability pensions or monetary compensation for damages sustained in accidents". 40% of mTBI individuals undergoing evaluations may be malingerers [113]. Tests carried out to evaluate malingered neurocognitive deficit (MNCD) include the Test of Memory Malingering (TOMM), tests capturing the evaluee's responses involving aspects that are under less conscious control, such as reaction time (RT) and brain activity using electroencephalograph (EEG). Malingering evaluees have slower RTs than both normal and brain injured control groups; [114]. Their RT patterns also differ resulting in a cognitive phenomenon, the "Stroop Effect" [115]. Findings were that honest (HON) normals and brain injured patients exhibited the Stroop effect, whereas malingerers

(uninformed/coached) exhibited an inverted Stroop effect. As TBI causes changes in EEG patterns, it in turn impacts on ERP markers of cognitive functions, including processing speed, sustained attention, performance monitoring, inhibitory control, and cognitive flexibility [116]. Among the ERP markers, the P3a can differentiate between those with TBI and malingerers [117].

In a malingered neurocognitive deficit (MNCD) study by Vagnini, 32 normal individuals (honest-HON; n = 16), normal individuals instructed to behave as malingerers (MAL; n = 16) as 15 patients with (TBI) were administered the Test of Memory Malingering (TOMM) and the Old-New Task test [118]. The time intervals examined for ERPs were N1, P1, N2, P2, N3, P3 etc. Comparison of the mean ERP amplitude values for each group suggested that HON and TBI showed the typical ERP Old-New effect while MAL differed. The effect for the Old-New task was intact for HON, reduced but trending towards significant in TBI, and absent in MAL. The differences between ERPs for frontal vs. posterior electrodes, HON had the strongest activity in the frontal area, for those with TBI strongest activity was in the posterior area, and MAL showed no significant difference between frontal and posterior activity. The frontal-posterior difference might be an effective indicator to identify malingerers.

In another study carried out by Neal latencies of memory-related brain potentials (sensitivity of 80% and specificity of 79%) were compared among individuals with moderate or severe TBI (n=14), and healthy age-matched individuals (honest; n=12 or faking memory deficit; n=15) [119]. Test of Memory Malingering (TOMM) and the Old-New Task test were used [57,58,120-126]. Bilateral fractional latencies of the ERP, P3a at frontal sites were averaged latencies = 396 ms malingerers and averaged latencies = 312 ms for true TBI in the frontal sites. Only malingerers showed asymmetrical frontal activity compared to the two other groups [120-126].

Challenges of EEG-based assessment of TBI: In mild TBI, 86% with an abnormal neurological examination have an abnormal EEG while only 23% of individuals with abnormal EEGs were abnormal on neurological examination [127-133]. These findings have been attributed to the order in which the brain heals; first symptom resolution, second clinical recovery and finally EEG patterns returning to normal. EEG abnormalities are more commonly seen in patients with durations of unconsciousness lasting more than 2 minutes (56%) than in patients with briefer periods of unconsciousness (17%) (127--133). EEG changes vary with individuals, the severity of head injury and changes in an EEG following a TBI can be restored to baseline as early as 15 minutes after concussion [127-133].

EEG-based markers to evaluate post-trauma neurocognitive ability: Assessment of cognitive impairment following a TBI ranges from evaluating pre-existing and new knowledge (acquisition and comprehension), attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving, decision-making, comprehension, production of language, temporal organization, conflict management, to cognitive and psychological (personality changes, impairments in processing social cues, emotions and in communication) aspects of behavioural disorders [134-157]. These cognitive issues together with accident phobia contribute to poor-quality of life, social and vocational outcomes following TBI account for 0.85 million requiring long-term rehabilitation and care in the United States [152,154-158].

Many of the cognitive impairments seen are attributed to EEG spectral changes [159-161]. Even mTBI is known to lead to EEG-detectable changes in brainwave patterns, connectivity, coherence, power and amplitude [65] and in neuronal network dysfunction [162,163]. Rapp in a review of 25 qEEG studies on mTBI found that though decrease in alpha power and increase in delta, beta, and theta power was often reported study findings varied greatly the first difference being attributed to differences in study aims and methodologies and the second due to the fact that no two TBI are the same. For example, only three of the 25 studies examined functional connectivity and coherence in mTBI and 9 studies examined the discriminatory ability of EEG in mTBI. O'Neil's study on EEGs discriminatory ability did not compare its ability to distinguish between mTBI versus controls instead the study examined sensitivity of the TBI-Index (94.7%) versus the New Orleans Criteria (NOC) and the TBI-index-plus-NOC (97%) in determining which patient with mTBI required a CT and which did not [68]. Evoked potentials (EP) both short and middle latency are used to predict coma outcomes and awakening in TBI while long-latency EPs are used to predict recovery of higher level cognitive function [92,153,164]. ERP associated with sensation (N100); perception (MMN); attention (P300), memory for own name (Early Negative Enhancement to Sound of Own Name); and comprehension (N400) are also used to differentiate between TBI and healthy controls. ERPs used to monitor cognitive impairment following TBI include:

a) The error-negativity/error-related negativity (Ne/ERN) and post-error positivity (Pe) used to evaluative control/performance monitoring [165,166].

b) Feedback-related negativity (FRN) is evoked following performance or response feedback, with a larger FRN indicating unfavourable outcome [165].

c) P300 amplitude and latency

d) Elicited using colours (red, green or darkness affect) is used to evaluate cognition and emotion post-TBI [167,168].

e) P300 elicited using images capturing facial cues is used to evaluate social behavior [155,163]. In a study of 13 individuals with moderate to severe TBI and 13 healthy controls P300 was measured following presenting of 30 pictures of angry faces and 120 pictures of neutral faces. TBI versus (vs) controls had a P300 latency of 486ms vs 416 ms ($p<0.005$), amplitude of 11.3μV vs 19.1μV($p<0.005$) and reaction time of 653ms vs 443 ms ($p<0.005$). Results indicate that following TBI patients had difficulty in detecting facial cues.

f) P300 amplitude and latency is correlated with duration of posttraumatic amnesia [169].

g) P300 elicited via three-stimulus oddball tasks demonstrated a decrease/suppression (in N2 and P3b amplitudes) in subjects ≥3years post-concussion compared to healthy controls and among multi-concussion athletes [136].

h) Gosselin in a study of 44 individuals with mTBI and 40 controls evaluated frontal: N200 and N350 and parietal: P200 and P300 amplitude and latency [139]. The propelling fact for the study was that 15% of individuals with sports related concussions/mTBI have persistent cognitive problems. The study examined working memory (WM) post-mTBI due to a motor vehicle accident (MVA) or sports injury. Chief findings were mTBI versus controls had significantly ($p < 0.05$) smaller amplitudes of both frontal N350 and parietal P300 and worse ($p < 0.05$) accuracy on WM task.

i) Auditory evoked potential (AEP) and visual evoked potential (VEP) stimuli (including facial affective stimuli) can differentiate between

healthy controls and TBI individuals and can be used to evaluate attention, detect emotion, and cognitive function [169-173].

j) Mismatch negativity (MMN) is used to evaluate automatic attentional processes and information processing. MMN is used to differentiate vegetative state from minimal conscientious state and in in predicting coma outcomes from coma [174,175]. The Halifax Consciousness Scanner (HCS) paradigm and the P300 are used to evaluate conscious awareness level [176]. Following severe TBI conscious awareness is often compromised which is usually using behavioral responses. In order to obtain a more objective idea of the patient's conscious awareness level a semi-automated electroencephalography system (HCS) was designed and evaluated in 28 sTBI patients and 100 healthy controls. Here to P300 latencies correlated significantly ($p<0.05$) with sTBI versus controls as well as with the clinical assessment scores.

Visually evoked stimulus at 750 msec post-stimulus is used to evaluate word retrieval which requires precise interactions between different brain regions [144]. In a study on word retrieval in 19 retired professional athletes with TBI and 19 healthy controls, both groups did not differ in accuracy or reaction time, however healthy controls showed significant differences between retrieval and non-retrieval conditions (between 750msec to 1000msec) while individuals following TBI showed no such difference [144].

Sleep disorders after TBI: Sleep disorders (hypersomnia, insomnia, parasomnia, daytime somnolence, changes in sleep patterns, sleep-wake schedule and deranged sleep architecture) common in TBI patients compromise rehabilitation and return-to-work. Their timely diagnosis and treatment will help facilitate the rehabilitation process [177]. Urakami studied the spindle activity in acute, sub-acute, and chronic stages of posttraumatic coma and in 60 adult patients following diffuse axonal injuries (DAI), with sleep-related complaints 3 months to 2 years following TBI [178-180]. Findings include; the four source where spindle activation occurs included the precentral (slow spindles seen) and post-central (fast spindles seen) areas in posterior frontal cortex (PFC) and parietal cortex of each hemisphere. When spindle distribution was symmetrically in amplitude all four cortical areas were activated. However, when spindles exhibited an asymmetric distribution with an amplitude differences of >30% between the hemispheres then temporal activation occurred. In the postacute stage (mean 80 days) frequency, amplitude, cortical activation source strength of spindle activities was significantly decreased while in the chronic stage (mean 151 days), spindles significantly increased, and no significant difference was found between normal subjects [180]. Cognitive functions also improved, with favorable 1-year outcome [179].

EEG patterns, neural connectivity and Z score biofeedback neurofeedback

In a study of gray matter-white matter normal control (n=25) subjects exhibited bimodal while TBI patients (n=31) exhibited unimodal gray matter-white matter histograms. More importantly while pixels of intermediate intensity (between grey and white matter) were at the border in controls, intermediate pixels were found both at the borders and in between grey and white matter in TBI subjects [181]. Functional impairments of the brain have been found to exist due to these and other changes in connectivity and network pathology [181,182]. The brain is thought to be composed of small-clusters with all clusters involved in a particular function interconnected in a manner that ensures optimum information processing [183]. Another theory it that the brain is both segregated into distinct regions based on function and yet it is integrated at the global level in order to promote information processing [183,184] with the prefrontal, frontal, and central sites all networked to ensure working memory (WM) and speed of information processing [185]. Specific functional networks exist for anxiety, language, memory, mood and pain [186-210]. The prefrontal cortex (PFC) is involved in working memory tasks, supplementary motor area (SMA) and anterior cingulate cortex (ACC) are implicated in "vocal-motor planning", the primary motor cortex (PMC) and SMA in movement and the "default network" in resting and contemplative states [211-219].

White matter (high speed relay system) when damaged following a TBI results in slower delta and at times even theta waves emerging [220-223]. Hypercoherence or hypocoherence is also seen depending on the damage following TBI. Gray matter (high plasticity) damage may initially cause spectral changes (increase in alpha causing cortical idling) but with time and healing the changes may return to ear normal (beta followed by gamma indicating active networks) [220-223]. The return to near normal of brain waves patterns can be stimulated by cognitive-behavioral/neurofeedback/ physical therapy interventions [224]. Transcranial magnetic stimulation (TMS), is a promising new tool used in treatment of TBIs like diffuse axonal injury (DAI) which account for 40% individuals with severe TBI [225-232]. Neurofeedback involves first identifying functional networks in the brain associated with a patients symptoms and then stimulating the impaired functional network [233-238]. A recent method used in EEG Neurofeedback is called *Z*-Score Neurofeedback here post-TBI individuals with symptoms/complaints are first compared with an age-matched population of healthy subjects to identify hubs and networks are unstable or dysregulated [233-238]. Using operant conditioning and reinforcement brain wave patterns in regions corresponding to the symptoms are stimulated until they go from exhibiting outlier patterns to closer to near normal Z-score patterns thus restoring equilibrium, increasing efficiency and the brain network and processing speed [233-238].

One review on EEG- and ERP-based markers of TBI found processing speed to be 1.54 times slower in TBI patients. Impaired perceptual and psychomotor processes were also observed [239]. P300 latency were found to reflect stimulus-processing time while contingent negative variation (CNV) reflected response-processing time. Following TBI impairment in processing of warning cues resulted in increased P2, N2 and P3 latencies as well as impaired attention to the warning cues indicated via reduced P2 amplitude compared to controls. As sustained attention is often a problem post-TBI one study used long-term focused attention (FA) meditation training to increase theta band consistency improving attention. The review also looked at ERP markers of performance monitoring, inhibitory control and cognitive flexibility following a TBI [239]. Another review focused on visual and auditory evoked ERPs. ERPs examined and elicited via visual or auditory odd-ball paradigms were N2, N350, and P3 i.e. P3a/P3b components. The characteristic amplitude reduction and latency increase pattern was seen among mTBI patients [240-242].

Conclusion

Traumatic brain injury (TBI) is a major health concern in terms of morbidity, impact on the work force, family life and income, disability, cognitive issues and mortality it causes. Electroencelaphalographs (EEG) like NeuralScan are essential tools at specific crossroads in TBI evaluation, management, treatment and rehabilitation (like predicting seizures post-trauma, defining severity of current and previous TBI, identifying malingerers, predicting TBI or coma outcomes, and

Z-score training via Neurofeedback).The added benefit of machines like Neuralscan in TBI treatment are that they are clinician friendly, versatile, reliable, robust, portable and cost-effective allowing for use at the site of the injury, in transit, for continuous monitoring (stationary and ambulatory) allowing for evaluation of brain wave patterns, EPs, ERPs, qEEG, topographical maps and frequency analysis, LORETA based source analysis and neurofeedback.

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