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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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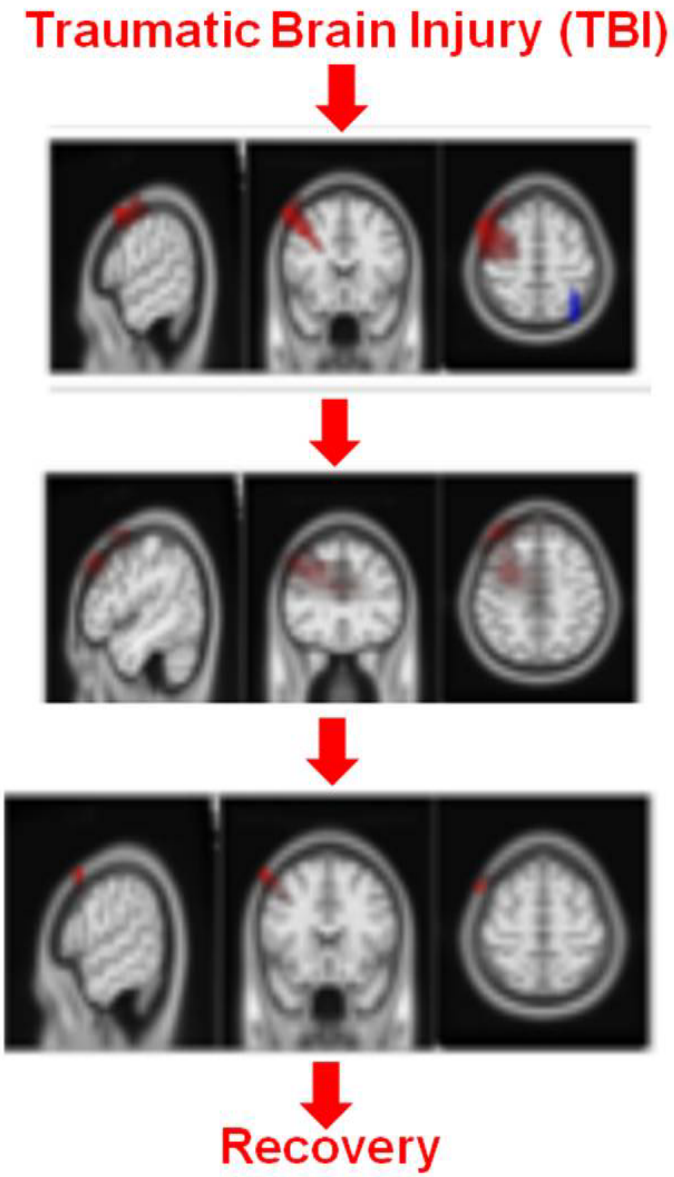

Figure 1. Working example of the dual use of eLORETA/sLORETA: To "track TBI" from injury to recovery, To "track Z-score retraining of the brain", LORETA Images taken using NeuralScan by Medeia

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

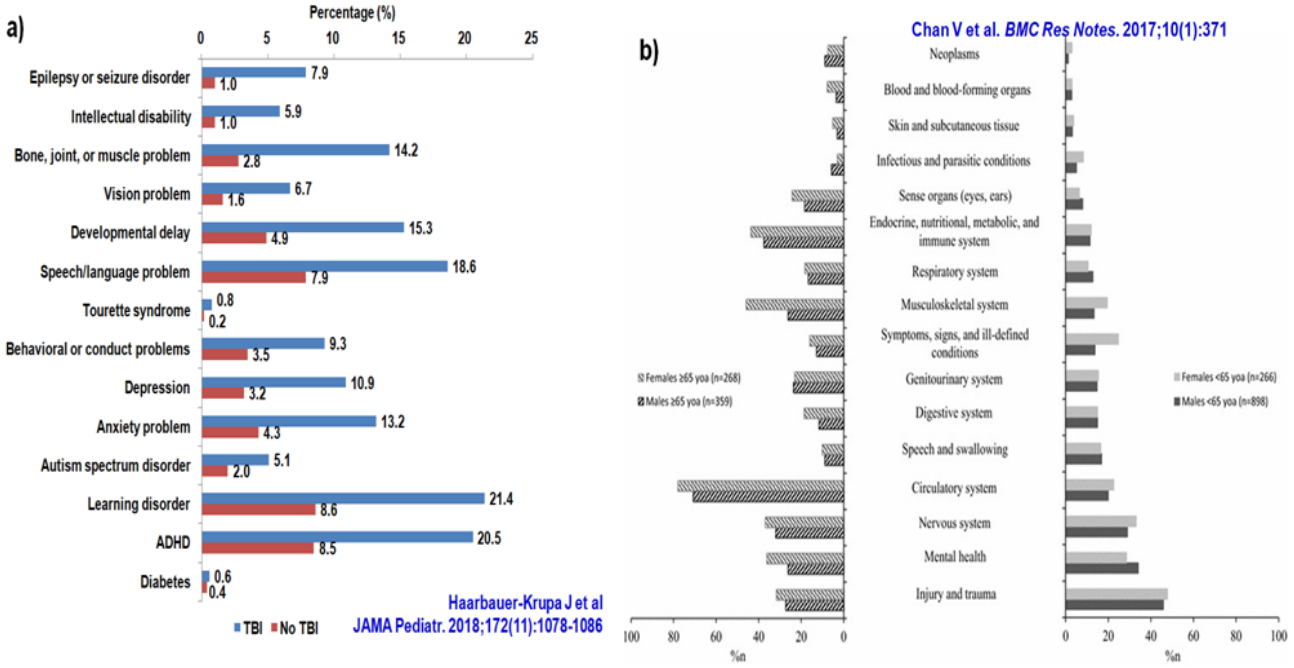

Figure 2. Prevalence of co-morbid conditions among a) Children (parent-reported), and b) <65 and ≥65 year-old Adults following TBI

Jain, K. K. (2008) Drug Discovery Today

https://www.nap.edu/read/13121/chapter/6 Chapter 3

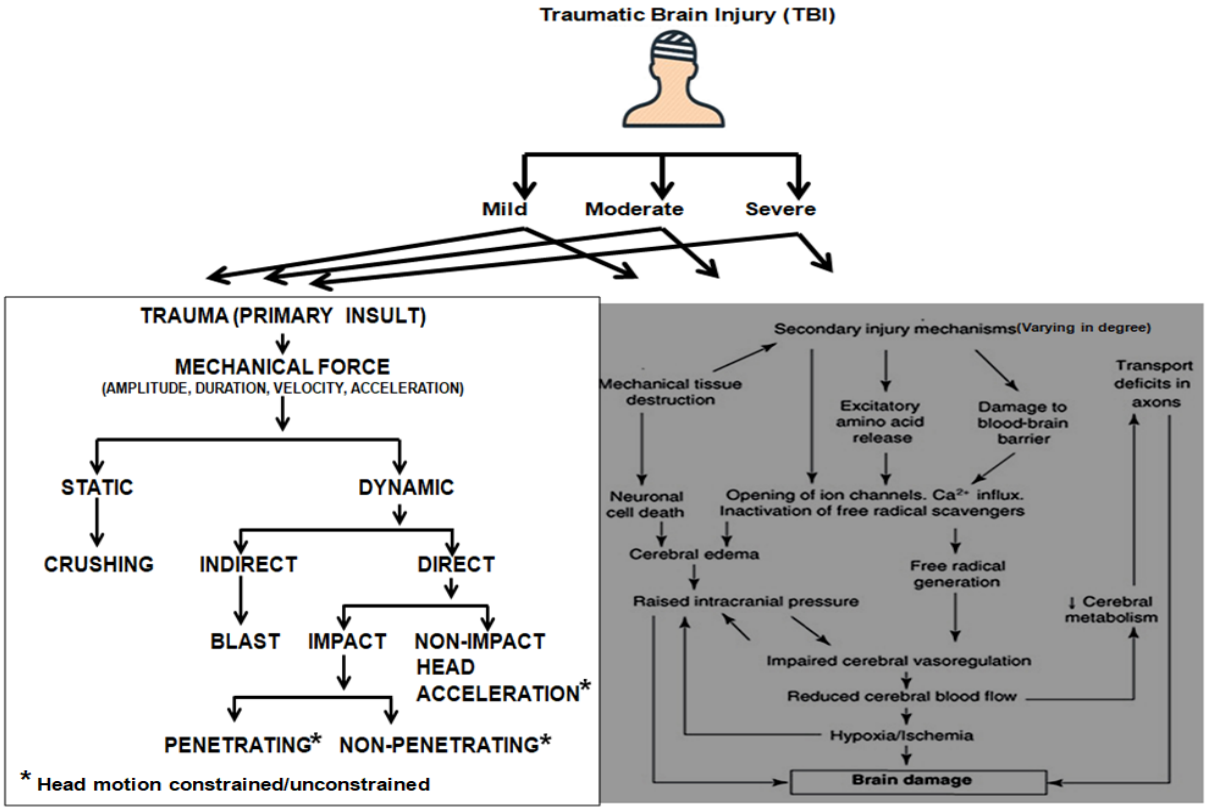

Figure 3. Trauma brain injury and its neuropathophysiology

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

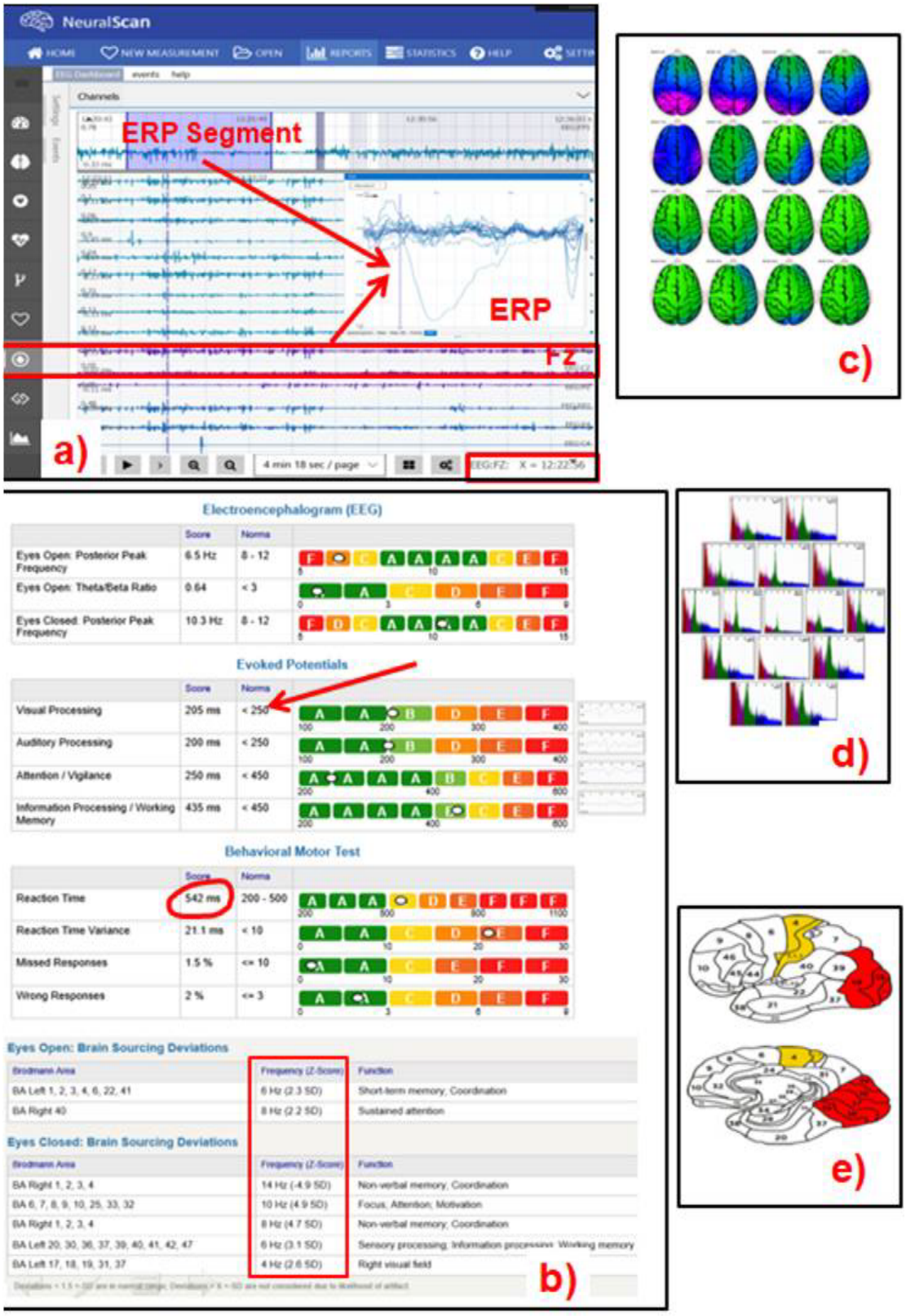

Figure 5. The potential of NeuralScan by Medeia in "TRACKING RECOVERY and brain RETRAINING" (Images of both features and reports that NeuralScan comes with; a)19-channel EEG tracing capturing ability, EEG tracing at rest, evoked potentials and event related potentials (ERP, b)Reports on visual and auditory 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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