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DIAGNOSING AND TREATING CLOSED HEAD INJURY:

(Exposing and Defeating the Mild Huge Monster)

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ABSTRACT

One of the leading causes of death and disabilities worldwide is brain injury. Most of the cases are mild and the prevalence of disabilities and its impact are not well known. In the last 20 years neuroimaging technologies have changed the way we approach traumatic brain injury (TBI), especially the mild injuries (MTBI), and its sequelae. New tools of treatment have been emerging in parallel with diagnostic technologies. Here, these non-invasive tools will be reviewed, especially those with therapeutic value, that have a direct impact on brain function, either on a passive way (operant conditioning, neurofeedback) or actively (transcranial electromagnetic stimulation). The main focus will be placed on EEG as a diagnostic and therapeutic tool on MTBI.

Mild traumatic brain injury, EEG biofeedback, neurofeedback, TMS, qEEG

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INTRODUCTION

Head injury or traumatic brain injury (TBI) is a very heterogeneous entity, with no standardized diagnostic system, in fact with a no established and official definition (see below). The two major causes of trauma are falls and automobile accidents; although other violent events have increased substantially in the last decade. Most of the patients are children (<5 years), young males (15-35 years) and the elder (>70 years) population. TBI severity depends on multiple factors, and classification has a long and complex history. It is still in debate, as well as are the consequences of the traumatic event in the short and long term [83]. An important project on this essential issue is lead by the National Institute of Neurological Disorders and Stroke, with support from the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, called NINDS Common Data Element (TBI CDEs) [107]. The TBI CDEs, through the Demographics and Clinical Assessment Working Group of the International and Interagency Initiative has formed an expert group that proposes the following definition: "TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force" [61]. An update can be found at the

TBI CDEs webpage and in Adelson et al. 2012 [1]. Also, an important paper by Ruff et al. [88] is recommended.

Despite decades of research, TBI is still one of the leading causes of death and disabilities worldwide, and, in some populations geographically and age-wise, it is the leading one. In the last century, evolution in the TBI field has been taking huge steps, and great advances have been made, especially in regard to intensive care resulting in improved rates of survival. The numbers of mild and moderate disabilities have gradually increased in the last 30 years, and there are no pharmaceutical options to mitigate those consequences[2]. With some exceptions, cognitive and psychological approaches have little or no treatment efficacy [3, 39, 120]. Excellent reviews and meta-analyses of cognitive training can be found elsewhere [19, 20]. There is no efficacious therapy by itself, so an integrative approach often is recommended. But, what therapies are the best to incorporate, remains a question. The Department of Veterans Affairs of the Department of Defense, through The Management of Concussion/MTBI Working Group, has published clinical guidelines for the management of MTBI [27]; also

other reviews and guidelines on the matter are recommended [57, 67].

For more than 40 years, operant conditioning using electroencephalography (EEG), also called neurofeedback (NF), has been used to treat resistant epilepsy, attention deficit disorder, learning disabilities, autism, depression, anxiety disorders, acquired brain injury sequelea (traumatic and vascular), and other disorders and symptoms [13, 21, 53, 72]. An overview of research especially relevant to MTBI is presented below. It is proposed that, although further research is badly needed, NF should be part of the integrative treatment for these patients.

EPIDEMIOLOGY

While you were reading the above during the last 5 minutes, almost 50 people died from head trauma worldwide-- almost 6 million a year [126]. In the United States (US) in the last 2 decades around 1.5 million people were treated in emergency rooms (ER) for traumatic brain injury (TBI) each year, and 80% were released from the ER. The incidence for MTBI is around 300-500/100,000. The number of persons who have suffered a TBI and did not seek

medical attention in a hospital setting or did not seek attention at all is unknown, but could be as high as 50% more than the officially reported number (near 3 million). It has been estimated that 5 to 6 million people in the US have long-term disabilities from TBI [45, 54, 89, 103]; and it is well established that MTBI is a risk factor for chronic degenerative disorders, such as Alzheimer and Parkinon's disease [23, 32].

The literature on the sequelae of MTBI is enormous, complex and contradictory. Some authors report that of those suffering MTBI, around 20% (up to 70% or as low as 5%) will experience symptoms of post-concussion syndrome (PCS) for more than a year, with the most common symptoms being fatigue, affective disorders, irritability, vertigo, attention and memory deficits, low verbal fluency, chronic pain (especially headache), anxiety disorders and sleep disturbances [12, 25, 41, 42, 47, 60, 65, 79, 90, 92, 97, 98]. Very often these after-effects are not considered significant, or are regarded as "psychological", meaning non-real, or at least non-biological, which seems illogical and ontologically wrong. The different criteria for diagnosis (DSM-IV and ICD-10) of PCS make it impossible to have acceptable epidemiologic data. A large study

reported that only 56% of the patients from more than 2,500 cases with MTBI had no symptoms 3 months after the injury [55]; on the other side, an elegant meta-analysis concluded that: "…to date six meta-analytic reviews, including the present one, found no evidence of a significant difference –between the MTBI groups and the control groups" [84]. There is an urgent need for integrative prospective studies in the general population to clarify the impact of MTBI and the variables that may contribute to PCS.

PATHOPHYSIOLOGY

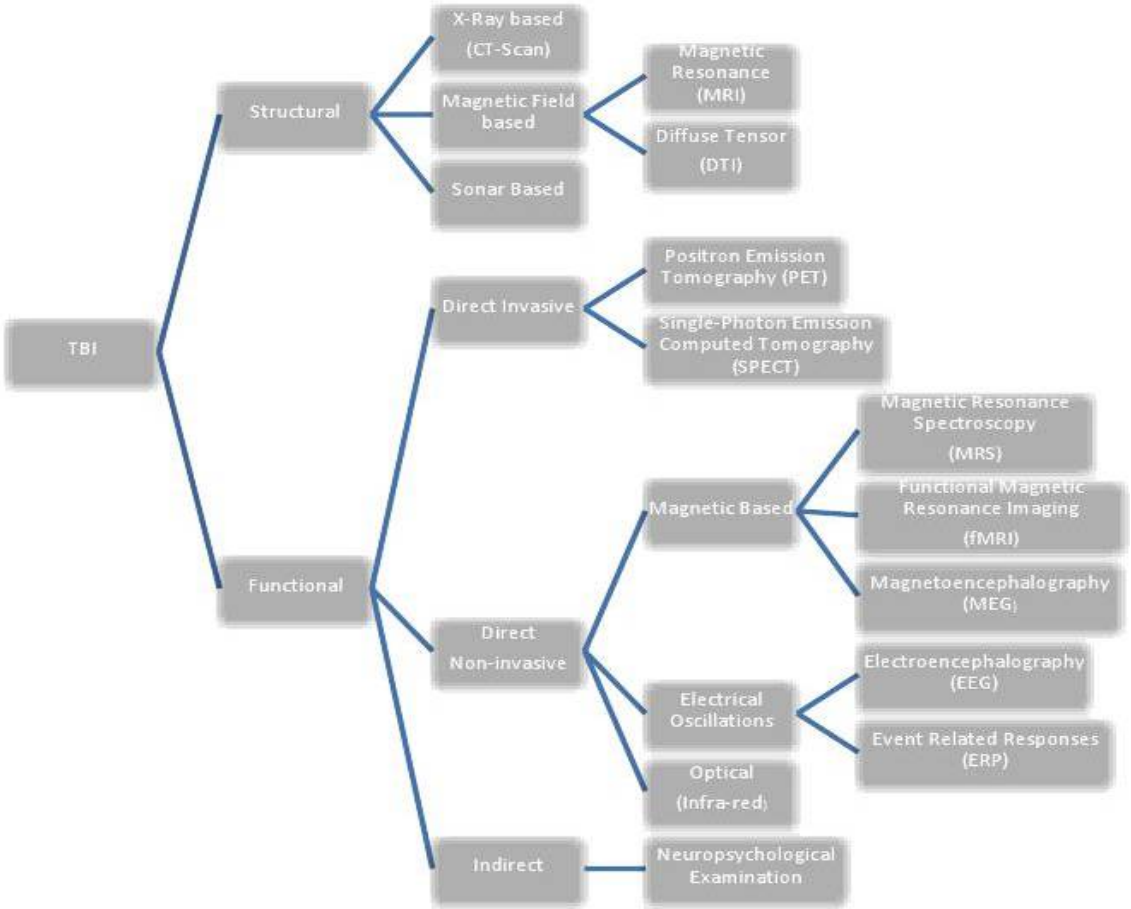
The forces (direct trauma and/or acceleration-deceleration and rotational) producing the primary injury could last as little as 100 milliseconds, but the secondary processes that follow can occur in the next hours, days and even months. It is known that the linear acceleration forces affect especially the cortex and the meninges, while the rotational forces have their major impact on the axons [diffuse axonal injury (DAI)], and the longer the duration of injury, the more damage produced . There is some damage to deep structures that could be explained by the stereotactical theory, which considers the spherical shape of the cranial vault as well as the vibrations produced at the moment of the injury and their

ability to generate secondary pressure waves. These waves travel and focus energy on the middle of the encephalic mass (deep cortical and subcortical structures). The trauma also has a systemic influence (adrenaline rush, hypoxia, arterial hypotension, hyperglycemia), which can effect the whole brain (seizures, cortical spreading depression, loss of autoregulation), and can act at the cellular level (release of excitatory amino acids, increase of inflammatory molecules, influx of calcium ions, cytoskeletal degradation and apoptosis). Each of these contributes to the primary and secondary processes of the brain injury at different scales and times [18, 36, 87]. The pathophysiological mechanisms are complex and is not the focus of this chapter but can be reviewed elsewhere [50, 58, 125].

DIAGNOSTIC TOOLS

The tools used for the diagnosis of brain disorders are illustrated in Figure 1.

Figure 1.



In this chapter the utility of EEG in the diagnosis of MTBI and PCS will be reviewed. For a more complete review of this topic the reader is referred to the special issue of Brain Imaging and Behavior from June of the present year [105], and to another recent reference [10], where neuropathological, neuroimaging and

neuropsychological findings and their correlations are thoroughly covered,

ELECTROENCEPHALOGRAPHY (EEG)

The ability to measure brain electrical activity took a revolutionary step when Hans Berger and his engineers made the first modern electrical amplifier of brain electrical activity. A few years before, in 1924 when still using a galvanometer, he planned to create a better apparatus. He stated, "I have cherished over 20 years that the device would develop into some kind of cerebroscope" [102]. The EEG captures the electrical changes produced by billions of synapses of the pyramidal neurons of the cortex. A way to imagine this is by taking a stadium (cranium) full of people (neurons) as a metaphor (dangerous, but necessary); and trying to imagine that we want to learn what is going on inside the stadium just by hearing what the people are doing through studying their singing and applauding (clapping). So, we use microphones and sound amplifiers to record the sounds coming out from the stadium. In this metaphor, let the singing of the people represent the *synaptic* potentials of the pyramidal neurons of the cortex. If a lot of people can join and synchronize with the same song; the greater the

volume (voltage) of the sound will be. Somewhat similarly, the more cortical neurons which fire in synchrony the greater the voltage of the brain's electrical oscillations, i.e., the greater their amplitude and power . The claps, however, are the *action* potentials of the pyramidal neuron, very fast and hard to synchronize, so are rarely heard. An essential aspect of the EEG is not about the song (frequency and volume) that is being produced, but about where and in synchronization with which others that song is being sung (corresponding roughly to what is involved in EEG connectivity measures such as coherence). It should be apparent from this metaphor that, just as the song and applause of persons in a stadium may be difficult to measure and, in any event, not tell the whole story of events in the stadium, so it is with EEG activity coming from a human cranium. The physiological and technical basis of EEG, should be well understood by readers who plan to use EEG measures, and such information can be found elsewhere [97, 122].

The analysis of complex information, such as the EEG, changed greatly in 1965 when the work of Cooley and Tuckey made possible a faster analysis of the Fourier Transform (FFT). From that time on,

the old, time consuming classical techniques used to quantify the EEG spectrum were replaced [29]. By the mid 80's the recording of brain electric activity using a digital amplifier was beginning to be customary, and a decade later it was the most used way to acquire and store an EEG in developed countries. Today, all EEGs are digital in nature. The digital EEG (dEEG) uses a different kind of amplifier, converting analog electric activity to a binomial language. Thus, dEEG today is really a mathematical transformation from its acquisition, to a computerized storage which can be called into forms of visual analysis and forms of quantitative analyses (qEEG).

Quantitative EEG (qEEG) refers to the process by which we can extract mathematical values from the digitized EEG, and use those numbers in multiple ways. This usually involves determining the amount of energy in single frequencies (or in frequency bands) across the full spectrum of a sample of EEG (spectral analysis). There are several mathematical methods to do a spectral analysis, but the most used is the Fast Fourier Transform method (FFT). These procedures also can be used to produce statistical values for a group of people on different EEG measures; thus enabling development of databases with normalized EEG measures against

which one can compare the EEG of others. This is referred to as norm referenced EEG (nEEG). Unfortunately, the terms digital, quantitative and normative are used in the literature as if they were synonymous; but not all digitized EEG is qEEG and not all qEEG is nEEG.

The medical guild has always undervalued the qEEG, claiming it is lacking in ability to localize sources of abnormality. Fortunately, the science of source localization has advanced greatly, and we can now say that EEG is another functional neuroimaging tool [62, 110]. For more on qEEG and nEEG the reader is encouraged to see the following references: [22, 33, 40, 43, 49, 80, 108].

DIAGNOSIS OF MTBI WITH EEG

The first paper reporting on this matter was by Jasper in 1940 [48], allowing us to say that EEG was the first neurodiagnostic tool to demonstrate brain damage after a TBI. For such a common pathology, research regarding the value of qEEG as a diagnostic tool surprisingly is very scarce. In this chapter focus will be put on the argument that qEEG (especially nEEG) should be the Gold Standard in the diagnosis of MTBI and PCS, in both its acute and long term phases. This reasoning is based on its low cost, easy

application and portability, high reliability and stability and, very importantly, its high sensitivity and specificity. For reviews the reader is referred to [4, 73, 108, 121].

Since the first reports of an EEG discriminant index for TBI by Thatcher and his group [111, 112, 113] and by Thornton [116], similar findings have been reported in a recent paper for a Spanish population using a qEEG discriminant function called the Sevilla Independence Index (SINDI) [56]. In this study, 81 patients suffering from acquired brain injury (TBIs or stroke) were almost 100% accurately classified with the SINDI, even though the mean time between injury and EEG recording was 22 months. The best discriminant values were connectivity measures of coherence and phase, demonstrating once more the original findings of Thatcher and collaborators. It is clear that qEEG measurements of connectivity can be found, which enable high sensitivity and specificity, far beyond 6 months post-injury. These phenomenon of long lasting effects have been called the Big Bump Theory, referring to how a single action, as the Big Bang, can generate huge and perpetual changes in this case in the brain (see "Big Bump Theory") [113]), especially in those patients with clinical symptoms.

In the last few years interesting research has been done, where pre-injury and post-injury evaluations of the same subjects found similar EEG abnormalities to those of Thatcher et al. The first study of this kind [14] assessed 61 college student athletes at high risk of TBI with EEG (19 channels), of which 30 actually suffered from a MTBI during the year following initial testing. A novel classification algorithm, "the support vector machine" (SVM), was applied to identify residual functional abnormalities in athletes suffering from concussion. The total accuracy was 77.1%. The discriminant function had a sensitivity of 96.7% (using linear analysis of SVM), and 80.0% (for nonlinear SVM). Another study from this research group [15] involved evaluating 160 college athletes with a 19 channel EEG prior to injury. Twenty-nine of the subjects suffered a MTBI in the next 6 months and were evaluated again 7 days post-injury. EEG source localization software was used and several connectivity methods were applied. Although most of the patients were asymptomatic by day 7, and back to baseline regarding neuropsychological measurements, qEEG analysis continued to show significant pre- to post- injury differences. The main abnormal findings were on connectivity and asymmetry measures. A year

later this group [16] recruited and evaluated 265 athletes from the Pennsylvania State University, with no history of MTBI. During the next 12 months everyone who suffered one concussive episode, was re-tested again around 30 days post-injury. All 30 of these MTBI subjects were asymptomatic and normal on neuropsychological testing by day 7, but on one EEG measure used (Shannon-entropy of the peak frequency shifting, SEPFS) there was not a return to normal. The same group in a more recent study tested 380 athletes before injury, of which 49 later had a MTBI (mild concussion). Post-injury evaluation revealed a correlation between rate of Alpha suppression and both balance and clinical recovery [99]. A good overview of this research can be found in [100].

Another series of reports of research in which athletes have been tested before injury has been published in the last couple of years. These studies have in common that they all used an EEG device (Brain Scope) with limited leads (4 frontal referenced to the ears). Compared to traditional EEG equipment, it is easier to carry and faster to apply on the patient, especially in the ER or any other emergency situation. The first research [66] involved 105 MTBI

patients and 50 controls (also patients from the ER, but with no brain-related emergencies). The EEG data were acquired during 10 minutes with eyes closed and at rest. One to two minutes of artifact-free data were analyzed using a TBI discriminant index (automatic analysis). The discriminant function had a high sensitivity (92%) for those patients with positive findings on a CT (complicated concussion), and only 34.6% on those with negative CT findings. The low sensitivity on the milder cases might be explained by the limited number of EEG channels used. In another interesting study [59], 396 college athletes were assessed before injury. Of those, 28 suffered a MTBI and were tested again on 3 occasions after injury: (the day of injury, 7 days and 45 days post-injury). They found that by day 7 the neuropsychological testing results were back to baseline, but qEEG findings were still abnormal, especially measures of coherence (low), asymmetries (high) and power (increased in the Beta band). It was not until day 45 that qEEG measures were not significantly different and approaching base-line values.

Another elegant paper [81], using the same index and methodology on 65 MTBI athletes, reported a severity discriminant between mild

and moderate concussion, with an accuracy prediction of 94% on who would return to play before 14 days. With a bigger group of 119 MTBI patients from multiple ERs, the authors [74] attempted to predict positive CT findings using the New Orleans Criteria (NOC). They reported that the qEEG TBI index had 94.7% sensitivity, while the NOC had 92.1%; but a main difference was on the specificity value, where the qEEG index was 49.4% against just 23.5% using NOC. Finally, Prichep [82] considering the argument that there has been no objective measurement tool for diagnosing MTBI, provides an overview of this new methodology (Brain Scope), and its high sensitivity (96%) and specificity (78%) with patients assessed at the ER who had positive findings on a CT scan. She concludes that such an automatic, portable and easy to use tool is of high utility in the acute clinical setting.

It is not feasible to review here the research findings regarding MTBI using other neuroimaging tools or their correlations with qEEG. For recent reviews on these issues please see [10, 44, 46, 69, 94, 100, 101, 123, 127]. Findings with these other tools do correlate with neuropathological findings, and with the physiopathology of MTBI. This is especially true for diffuse axonal

injury which strongly correlates with qEEG coherence and phase lag measurements and with DTI [115]. Although a lot remains to be done regarding the diagnosis of MTBI in its acute phase and especially in its chronic phase (or PCS), there is no doubt to the author that the best paraclinical tool today for aiding in the diagnosis of MTBI and PCS is qEEG.

TREATING THE "SILENT EPIDEMIC"

As we need integrative diagnosis, we also need integrative treatment [91]. There is no single therapeutic answer for most human disorders, and brain disorders are no exception. The most used therapies to handle PCS are cognitive training, behavioral and educational therapy and other rehabilitation programs such as speech and motor therapy. The PCS diagnosis is "foggy", unspecific and based on weak pathophysiological grounds. This makes certain therapies very attractive to try to implement, especially those that directly modify brain function, either by actively stimulating the cortex or passively guiding (conditioning) brain activity based on a neurophysiological data.

EEG BIOFEEDBACK

Any physiologic function of our body that can be measured can, in principle, be conditioned to a stimulus, and, therefore, be manipulated. This is the principle of any operant conditioning therapy using biosignals. EEG biofeedback, a form of brain-computer interface (BCI), and commonly called neurofeedback, has been used in treating multiple disorders [11]. NF involves an operant conditioning learning process that utilizes qEEG data as the behavior to which a stimulus is to be correlated, with the goal of modifying specific brain function and its cognitive and behavioral effects. It is important to mention that NF training also can be accomplished other tools, such as NIRS, MEG or fMRI. To provide NF in a proper manner, an accurate and complete diagnosis has to be given, for which nEEG [38], and a previous expert visual analysis of the EEG tracings is considered essential.

The research on the efficacy of NF with MTBI-PCS is very limited, and most published data have important shortfalls such as small number of subjects, heterogeneous groups, no control group, and/or no objective measurements. This makes it impossible to determine present efficacy of NF for the treatment of PCS. Since the first review [107] 12 years ago where specific suggestions for future

research were given, there has not been a single Class I (Prospective, randomized, controlled clinical trial in a representative population) published paper on the issue. Even more surprising is the fact that in indexed publications, more reviews have been published than research articles. Only around 10 publications (2 of them indexed), and 4 reviews [28, 119, 120, 121] have been published since 2000.

The first reports seems to be those of Ayers [6, 7], with patients ranging across the full spectrum of severity. Positive results were reported in most of the cases, using different NF protocols. In most cases treatment involved reducing slow frequencies (<7Hz) and reinforcing 15-18 Hz. For a review of these series of cases please see Ayers, 1999 [8]. It is important to say that this research was never published in a peer reviewed publication, and any conclusions have to be taken with reservation. The reports of Thornton and collaborators [117, 118, 119] involved a total 8 TBI patients in the 3 publications. There were consistently positive findings, but the small numbers and many research design weakness in each of one of these reports only permit one to conclude, along with the authors,

that NF seems a promising tool in the area and may be effective, but much more research needs to be done.

To the author's knowledge, since the last review in 2009 [121] only 2 papers have been published, and one of them used an unusual "innovative electroencephalography (EEG)-based therapy" [96], the Flexyx Neurotherapy System (FNS). The first report is by a group in Macedonia [129], in which 6 patients with more than 2 days of coma (all severe TBI) were treated 2 to 5 years post injury. The authors measured cognitive function with the Wisconsin Card Sorting Test (WCST) and the Stroop Color Word Test. They also acquired EEG data, and used the Human Brain Institute Database (HBID) for nEEG. Of these 6 patients, one did not have any cognitive sequelae, and the authors failed to explain why was this subject was taken into account. Most of the subjects were young (15-19 years old) and well functioning before injury. NF therapy was applied twice a week for 20 sessions of 40 minutes each, where 4-7 Hz power was inhibited and 10-14 Hz power increases were rewarded. Before the NF session, a 15 minute session of peripheral biofeedback (BF), based on skin conductance or heart rate variability, was applied. A complex EEG measurement considered indicative of arousal,

(referred to by the authors as "Brain Rate") was acquired, and all TBI patients had a Brain Rate index lower than the norms (HBID). The results reported by the authors are vague and general. One of their conclusions was: "Along with the changes in EEG spectra, improvements of general mood, quality of sleep, and cognitive abilities were obtained. Four of our patients were considerably improved and continued with studies…". Only one patient did not show any improvements, and changes in the other a reader must suppose were not significant. Although the patients were reported as improved, nowhere in the paper was it explained how they measured mood and quality of sleep. Also, as mentioned before, one of the patients did not have any cognitive problems, and is not the one who did not show any improvement. So, a reader is left to believe that this patient did improve in his or her cognitive function, although having an IQ score of 140 post-injury. No objective data is given on the neuropsychological testing post-treatment. I fully support their final conclusion about there being a need to assess the efficacy of NF in TBI patients compared to other treatment modalities in larger samples.

In the spring of 2012 Nelson and Esty [68] using the FNS which they described as "a novel variant of EEG biofeedback" recruited 7 veterans with persistent PCS and post-traumatic stress disorder (PTSD) resistant to medications. The FNS is not a conventional biofeedback process, and, in fact, is not totally an operant conditioned learning activity, because a very weak electrical signal is returned to the patient based on EEG activity [96]; this method is known also as LENS (Low Energy Neurofeedback System), although. The patients were administered the Neurobehavioral Functioning Inventory (NFI) and the PTSD Symptom Scale (PSS) before and after treatment. The participants received 2-3 sessions per week for a total of 22-25 sessions. Of the 7 subjects, only 5 completed treatment and post-treatment testing. Of these 5 patients 2 discontinued therapy before the 25 sessions (13 and 17 sessions respectively) because of improvement of symptoms to "minimally acceptable levels", meaning they dramatically improved. There was significant improvement on almost all measurements of the NFI and PPS. All subjects, if taking medication, substantially decreased their medication doses post-treatment. As the authors concluded, even when good results are found, these should be

taken as preliminary results and larger, controlled and randomized studies are warranted.

The total number of TBI subjects treated in studies which have been published in peer reviewed publications is no more than 150. And, no more than 40 of these patients were in indexed publications (that is, indexed in Medline); this makes NF a very weak option treatment evidence-based wise. Furthermore, of those subjects not all were MTBI-PCS patients. Although the efficacy of NF has been established as a treatment in other disorders [5, 104] as well as for improving performance in healthy subjects [37], the *assumption* it is as efficacious with PCS patients is just that, and scientific proof is needed. It is to be desired that in the near future more research will be completed involving larger number of subjects, appropriate control group, and proper diagnosis and evaluation. This could change the present situation to one of a well established, evidence-based reality concerning the efficacy of NF in MTBI-PCS.

TRANSCRANIAL STIMULATION TOOLS

With some exceptions where FDA approval has been given and efficacy has been proven [94], the use of non-invasive brain

stimulation (NIBS) is still considered experimental. This includes its use with MTBI. In fact, it is very much like the case of NF, where clinical research have been published on many neuropsychiatric disorders, although their cellular and molecular mechanisms are not well understood. For both modalities the potential to promote neural-synaptic plasticity has been reported [9, 75, 85]. NIBS involves different tools that use either electric or magnetic forces to stimulate the cortex from the outside of the cranium [see (78) for an excellent review]. The idea of using electrical stimulation on the body to improve it has been documented since the time of the ancient Egyptians [102].

Transcranial magnetic stimulation (TMS) or repetitive TMS (rTMS) was introduced almost 30 years ago into the clinical setting, and since then thousands of papers have been published. Its application on TBI patients is in the initial phase, with a handful of publications, most of them involving severe and comatose patients. A first review [76] concluded that, based on the data presented in that paper, TMS deserved to be investigated on TBI patients. The authors mentioned that an initial study using a modified rTMS technology was being planned using severe TBI patients during coma recovery.

In fact, this was done, and results published on a single case study [77] showing promising but inconclusive results.

There was another recent single case report [74] involving a young male with hypoxic encephalopathy who was in a prolonged coma and both NF and TMS were provided. Small progress on neuropsychological testing and ERP results after NF (Beta training), and major improvements after a TMS program were reported. It seems clear that, while NIBS therapies should not be the only treatment for TBI rehabilitation, it can enhance and potentiate other therapeutic programs. And, although a lot of work remains to be done, seems like a new era in neurotherapeutics is on its way. For excellent reviews the reader is referred to [26, 66, 124].

CONCLUSIONS

In a country were at least 2 million persons annually suffer from a MTBI and at least 10% of them will have permanent sequelae with possible effects on their quality of life and their aging process [24], it is imperative that biologically-based diagnostic and prognostic tools be developed and used. There is no doubt in this author's mind that qEEG is an excellent tool, and the best available today, to

aid in the diagnosis of MTBI and PCS. It is important to mention here that research is needed to differentiate between MTBI-PCS and other neuropsychiatric disorders with similar symptomatology (depression, PTSD, dementias, sleep disorders) that are not secondary to injury. However, it is very possible that similar pathophysiological mechanisms are shared in these disorders, independent on the cause (trauma, vascular insults, endocrinological disorders, etc.). As with all diseases, especially the chronic-degenerative disorders, it is well accepted that the cause is the sum of multiple variables. Therefore, it is ideal to have an integrative diagnosis [34, 71], where genetic markers [51, 64], simultaneous multi-neuroimaging tools, [10, 52], molecular markers [31, 86], neuropsychological testing, clinical picture, personal history and common epidemiological data are fused in a single database. This could enable finding correlations that would give reliable information for an etiopathogenic diagnosis, personalized treatment and accurate prognosis.

In the last decade important research applying NF in neuropsychiatric disorders has been conducted and some progress has been made regarding MTBI. This is the reason that we conclude

that NF is a promising therapy inside an integrative management program for PCS. However, Class I evidence for this still is needed. New technology permitting NF training based on data from real-time qEEG (as in Z-score NF), and/or from low resolution brain electromagnetic tomography (LORETA), appear to be more powerful techniques of NF [110, 117], and increasingly are being applied. Hopefully, in the near future publications will come from rehabilitation programs such as that at Fort Campbell in which soldiers are being extensively tested with behavioral and psychological evaluations prior to implementation of LORETA Z-score NF [110]. Further research specifically focused on this type NF with MTBI-PCS, is needed in order to determine its efficacy and possible superiority over conventional (surface-amplitude- based) NF.

The use of TMS and other extra-cranial stimulating therapies [30, 78] opened a new window on the field of clinical neuroscience, and, along with neuroimaging technologies, has promise to revolutionize the field of brain research. Although the efficacy of NIBS tools in brain injury in general is still unknown, and a lot of questions on technical details are debated, there is no doubt that these

technologies have an important impact on brain function and microstructure. In the near future more data on their applications in TBI can be expected, and hopefully soon enough will be taken into the clinic to become part of the therapeutic arsenal against this "silent epidemic" that is harming millions of the young people, who are the future essential pillars of our society.

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