The role of pulsed magnetic fields in the management of concussion and traumatic brain injury.

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Traumatic brain injury (TBI) is a complex clinical phenomenon. (*Raji*) The classic designations of mild, moderate, or severe TBI are based on the acute clinical presentation and do not necessarily predict the long-term outcome. The long held assumption that the mild forms of this condition recover rapidly and without consequence is not supported by more recent literature. The effects of several mechanisms for TBI lead to neurophysiological changes, cellular depolarization, and apoptosis that occur on a continuum and can progress over a protracted period of time. Mild TBI (mTBI), particularly repetitive mild TBI, can create neuropathology that contributes to long-term increases in morbidity and mortality. People with TBI have an increased risk of death by suicide (3-4 times greater), higher suicide attempts and suicide ideation. (Simpson) Repetitive mild TBI, also known as ‘‘repetitive concussion,’’ can lead to a progressive deposition of tau protein in neural tissues (tauopathy), now known as chronic traumatic encephalopathy (CTE). At this point this is an irreversible and deadly condition.

The diagnosis of TBI, particularly mild TBI (mTBI), remains a challenge clinically. There is overlap between the symptoms of mild TBI and posttraumatic stress disorder (PTSD). Symptoms can include headache, dizziness, irritability, sleep disturbances, sensitivity to light and noise, impulsivity, judgment problems, visual disturbances, emotional outbursts, depression, and anxiety.

Imaging using MRI, neuroimaging, is one focus to identify changes in brain function. Changes in brain structure are a late change in most neurological disorders, such as dementia. Structural changes able to be seen on MRI are frequently insensitive to the earliest changes seen in disease progression.

In TBI, a recent study showed that changes in cerebral blood flow (CBF) preceded changes in MRI diffusion tensor imaging (DTI). CBF abnormalities persist even in chronic TBI. Single Photon Emission Computed Tomography (SPECT) can identify early changes in neurological diseases through regional CBF. This may be predictive of damage. But, SPECT is not widely available, expensive and not covered by insurance.

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Background

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Pathophysiology

TBI is common in contact sports. mTBI, or concussion, causes functional disturbance and injury to individual nerve fibers (axonal injury) rather than gross structural brain damage, affecting larger regions of nerve fibers that are damaged and not likely to be seen by the human eye or in most imaging studies. (Ling) The extent of neuronal or axonal damage has to be significant to be seen on even the most sensitive imaging systems. This is why MRI is typically negative.

Concussion symptoms tend to develop acutely but resolve within a week or two. Severe concussion can also lead to loss of consciousness. Despite the transient nature of the clinical symptoms, functional studies show that the disturbances seen with concussion take over a month to return to baseline and neuro-pathological evaluation shows that concussion-induced functionally important brain axon damage may persist for years. Focal axonal injury and spots of micro-hemorrhage lead to the deposition of focal tau-positive neurofibrillary tangles (NFTs). These in turn are a common source of Alzheimer's disease or dementia. So, CTE-tau pathology is a result of acute TBI-related axonal injury, loss of microvascular integrity, breach of the blood brain barrier, resulting inflammatory cascade and activation of microglia and astrocyte. These changes are the primary targets for considering alternative therapies, such as, pulsed electromagnetic field (PEMF) therapies.

The development of CTE from a single TBI or multiple small, unrecognized TBI's, is simply like removing bricks from the wall of a house. Sometimes only one is removed at a time and sometimes sections are removed at a time. Obviously, the more bricks that are removed at any given time the more obvious the damage is. By the time symptoms of CTE become obvious many bricks have been removed permanently, lessening the ability to be able to create any impact on the condition or slow or reverse the progression of the condition.

The lesson from all this is that early, frequent and continuing intervention is often necessary even with the earliest concussions/TBI's with minor head insults. The brain is the hardest organ in the body to recover structure and/or function without outside stimulation and support from supplements and nutrition.

Current Approaches to Treatment

Therapies, aimed at improving functional recovery, remain the mainstay of treatment. (*Hoffer*) Therapies do not fundamentally address recovery of the neurological physical injury itself. This latter deficiency must be more extensively evaluated, in terms of feasibility and effectiveness.

Acute concussion is currently managed somewhat differently than managing the symptoms of PCS or evidence of persistent concussive damage. (*Choe*) Symptoms are typically short-lived, and may

correlate to physiologic changes in the acute period after injury. There are many available tools that can be utilized on the sports field sideline as well as in the clinical setting for assessment and diagnosis of acute concussion. Neurocognitive testing may be helpful in the subacute period. Management should begin with removal from risk if a concussion is suspected, and once diagnosis is made, education and reassurance should be provided. Once symptoms have resolved, a graded return-to-play protocol can be implemented with close supervision and observation for return of symptoms.

Management should be tailored to the individual, and if symptoms are prolonged, further diagnostic evaluation may be necessary. While most people have clinically apparent recovery from their concussions, it is very difficult at this time to predict who will have persistent symptoms. If acute concussion is not managed aggressively, there is a missed opportunity to prevent the physical, psychological and economic effects of more subtle nonclinical damage later in life. This again underscores the need for more subtle diagnostic tools, that are easily and noninvasively applied, and other physical modalities to help with structural damage in the brain itself.

Despite the above goals, and given the evidence available to date, treatment and management of mTBI/MoTBI has been outlined in several guidelines. Because there are significant gaps in the evidence, there is considerable variability in the quality of guidelines addressing mTBI. (*Berrigan*)

The US Department of Veterans Affairs/Department of Defense (*VA/DoD*) guideline states that the management of patients who present with symptoms following a concussion/mTBI injury should focus on promoting recovery and avoiding harm. A patient-centered approach is used to provide reassurance and motivation. Patients with prolonged symptoms are suffering, distressed, and in need of guidance, education just to bring stuff in here, support, and understanding. The majority of patients with concussion/mTBI do not require any specific medical treatment. Substantial short-term and long-term neurologic deficits, similar to those following concussion/mTBI, can be caused by blast exposure without a direct blow to the head. The symptoms associated with PCS are not unique to mTBI. A gradual resumption of activity is recommended. If physical, cognitive, or behavioral complaints/symptoms re-emerge after returning to previous normal activity levels, a monitored progressive return to normal activity as tolerated should be recommended.

Based on current evidence, education of patients and their families is the best available treatment for concussion/mTBI and for preventing/reducing the development of persistent symptoms. Treatment of somatic complaints (e.g. sleep, dizziness/coordination problems, nausea, numbness, smell/taste, vision, hearing, fatigue, appetite problems) should be based upon individual factors and symptom presentation. Headache is the single most common symptom associated with concussion/mTBI and assessment and management of headaches in individuals should parallel those for other causes of headache. Medication for ameliorating the neuro-cognitive effects attributed to concussion/mTBI is not recommended. Medications for headaches, musculoskeletal pain, or depression/anxiety must be carefully prescribed to avoid the sedating properties, which can have an impact upon a person's attention, cognition, and motor performance. Treatment of psychiatric symptoms following concussion/mTBI should be based upon individual factors and the nature and severity of symptom presentation, and may include both psychotherapeutic and pharmacological treatment modalities. In patients with persistent post-concussive symptoms (PPCS), which have been refractory to treatment, consideration should be given to other factors including psychiatric, psychosocial support, and compensatory/litigation.

Canadian guidelines have been published in 2012 to aid health care professionals in implementing evidence based, best-practice care for the challenging population of individuals who experience persistent post-concussive symptoms (PPCS) following mild traumatic brain injury (MTBI). (*Marshall*)

Effectiveness of Current Treatment Approaches

Because most current treatment approaches involve education, various individualized therapies and symptom management, there is a significant need for consideration of other safe and non-toxic modalities, which may help to accelerate brain repair, other than a wait-and-see approach. Transcranial magnetic stimulation is one such potential therapeutic approach.

Neuro-enhancement uses neuroscience-based techniques for enhancing cognitive function by acting directly on the human brain and nervous system, altering its properties to increase performance. (*Clark*) These include several methods, including transcranial electromagnetic stimulation methods.

PEMFs as a Potential Solution

PEMF Biologic Effects

Based on the neural pathology seen with TBI, that is, axonal injury, loss of microvascular integrity, breach of the blood brain barrier, inflammatory cascade and microglia and astrocyte activation, PEMF therapies address these physiologic changes. Earlier intervention would produce better results than later intervention.

The use of PEMFs to affect brain function - TBI and non-TBI studies

So, what is the science on the use of PEMFs to effect changes in the brain, in general, or, more specifically, in TBI? PEMFs are known to penetrate all the tissues in the body equally. PEMF stimulation may be low to medium or high intensity. Even outside TBI, there are significant brain neural effects from magnetic field stimulation.

Non-TBI – General Brain Effects

PEMFs have effects on brain neuro-transmitter levels (Zecca), affect monoamine function (*Sieron*), circulation (*Bartko*), reaction time (*Blackman*), stem cell and growth gene factors (*Goodwin*), charge displacement from neuronal membranes of cortical neurons. (*Persinger*) Less invasive PEMF procedures are preferred.

With deep brain electrical stimulation, an invasive procedure, 15 billion neurons could be affected, about 10% of all neurons in the brain. Even a very weak PEMF will stimulate about 25 billion neurons. Electrical stimulation requires massive invasive intervention; PEMF requires only a quiet chamber, some external solenoids, and a magnetic field generator.

PEMFs produce rapid mood elevation in depressed patients with bipolar disorder (BPD) (*Rohan*), other depression disorders. (*Leuchter, 2013*) rTMS is a robust and FDA approved treatment for MDD. rTMS enhances neuroplasticity, entrains and resets brain cell oscillators, between the thalamus and the cortex, normalizes regulation and facilitates reemergence of natural cerebral rhythms, and through this mechanism restores normal brain function. Therefore, rTMS can be administered as a low magnetic field strength sinusoidal waveform, broadly to multiple brain areas simultaneously.

Treatments for major depressive disorder (MDD) act at different biological levels, ranging from individual brain cell connections (synapses) to the brain as a whole. (*Leuchter, 2015*) Antidepressants ultimately work through similar cell connection mechanisms. Neuromodulatory treatments such as PEMF resulted in similar changes. As a result they appear to help neuroplasticity related to neurodevelopment, learning, and memory, as well as medication and neuromodulatory treatment for MDD.

Low-field magnetic stimulation also may be useful for treatment of MDD, with fewer treatment-

related side events. (*Leuchter, 2015, May*) Patients have significantly greater improvements in depression scores. There are no differences in adverse events.

ELF-MF stimulation applied to the head (*Amirifalah*) in healthy women for only 9 minutes. Exposure to the top of the head at 10 Hz was useful in the treatment of anxiety. Low intensity PEMF stimulation may enhance memory processing and attention, (*Basar*) and a state of relaxed wakefulness. (*Niedermeyer*)

Moderate intensity PEMFs (200 mT) have been shown (*Cook*) to enhance alpha relaxation activity and may need to be continued for longer times to obtain more enduring benefits.

Traumatic Brain Injury

The brain mounts a robust and long-lasting inflammatory response to injury that involves IL-1, a pro-inflammatory cytokine and major mediator of the post-traumatic inflammatory response. (*Rasouli*).

In a very important study, Rasouli et al explored whether PEMF signals could alter the course of IL-1β production in rats having head injuries caused by weights dropped on the head (contusion model) or penetrating needle-stick brain injuries. IL-1β levels in cerebrospinal fluid (CSF) were proportional to injury severity in the contusion model. PEMF applied continuously for 5 min every 20 min for 6 hrs, or for treatments longer than 6 h, treatment was set at 5 min every 20 min for up to 9 days right after the injury. PEMF treatment reduced IL-1β levels up to 10-fold in CSF within 6h after blunt injury and also significantly suppressed IL-1β within 17-24h after penetrating injury. This study clearly showed the reduction of inflammation following head injury by a PEMF signal.

Headaches improved following concussion treated with PEMfs for only 0.5 hrs (*Grunner*).

Psychological depression following TBI often does not respond completely to antidepressant drugs. This type of depression may be associated with subclinical, complex partial seizure-activity within the brain that continues for months to years after apparent neurological and behavioral "recovery." (*Baker-Price, 1996*) Even a weak PEMF across the temporal lobes once per week for 5 weeks produced a significant improvement of depression and reduction of phobias.

High intensity – repetitive transcranial magnetic stimulation (rTMS)

High intensity transcranial magnetic stimulation (TMS) a low is being increasingly studied in many neurological applications as a painless method to stimulate the brain. (*Pape*) Repeated applications of TMS can influence brain plasticity and cortical reorganization through stimulation-induced alterations in neuronal excitability. Existing evidence has demonstrated positive outcomes in people with motor disorders and psychiatric conditions.

rTMS has shown improvement in patients with posttraumatic stress disorder (PTSD) (*Cohen*) and pain (*Moisset*), and improvement of interregional integration in the brain with improvement in related behavior (*Plewnia*), and depression. (*Leuchter, 2015*) They found a 27% reduction in a depression score.

rTMS can also improve cognitive function in Alzheimer's disease (AD), a long-term consequence of TBI. (*Liao*; *Lee*). rTMS improves brain activity through connected brain network by improving regional cerebral blood flow (CBF), not only at the stimulation site but, most importantly, in farther regions functionally connected with this site. Improving CBF in areas with reduced blood flow, as seen in traumatic brain injury and other mental health conditions, can facilitate healing of the brain tissues and improving brain function. (*Leuchter, 2013*) rTMS stimulation of the left frontal cortex increased alpha EEG activity, enhancing relaxation and stress reduction. (*Okamura*) Treating

formative brains with PEMFs needs to be done with care because of the risks involved. In a study high intensity magnetic fields on neonatal rat brains (*Diamond*), eight out of nine brain areas were thicker, suggesting that exposure of neonatal rats to high intensity magnetic fields either had no effect or, with a higher intensity magnetic field, actually promotes brain cortex development.

While the above clearly indicates significant improvements in various aspects of brain function outside the setting of TBI, studies with TBI have clearly shown benefits as well. Headache is one of the most common debilitating chronic pain conditions in patients with mild traumatic brain injury. Conventional pharmacological treatments have not been shown to be effective in alleviating debilitating mTBI-related headaches (mTBI-HA). Therefore, the development of an innovative non-invasive therapy in managing mTBI-HA is needed in the field of pain management. Patients treated at a VA facility with established diagnoses of mTBI-HA (), had average post-rTMS headache intensity reduced by 53%. The average headache exacerbation frequency (episodes per week) was reduced by 79% with some patients reporting complete resolution of severe headache episodes. For those with persistent headache exacerbations, the average duration and intensity of these exacerbations were reduced by 50% and 32%, respectively.

Alcohol use disorder (AUD), mild traumatic brain injury (mTBI), and posttraumatic stress disorder (PTSD) commonly co-occur (AUD + mTBI + PTSD). (*Herrold*) These conditions have overlapping symptoms which reflect overlapping neuropathology and can exacerbate symptoms. rTMS appears to be an ideal treatment for these co-occurring conditions as it has been used with each one alone.

mTBI is typically followed by various post-concussive symptoms (PCS), including headache, depression, and cognitive deficits. In 15-25% of cases, PCS persists beyond the usual 3-month recovery period, interfering with activities of daily living and responding poorly to medications. rTMS (*Koski*) stimulation reduced PCS scores by 15 points and increased fMRI assessed brain function. rTMS was safe and tolerated by most patients with mTBI.

Safety and Risk of PEMFS

When PEMFs are suggested for the treatment of TBI, or for that matter, aimed at the brain for any reason, concern about safety and risk is automatically raised. There is much evidence to suggest that there is minimal risk with a large upside potential as seen from the literature review above.

Macaque monkeys were exposed 18 hr/day for 21 day periods. (*Wolpaw*) The animals remained healthy and active throughout exposure period, and no striking or consistent changes were noted in appearance, demeanor, or behavior. Gross examination of the brains and meninges of five autopsied animals were normal. There were no significant systemic metabolic alterations associated with field exposure. In rats who were electrically stimulated to produce seizures, PEMFs had an inhibitory effect on the generation of seizures. (Ossenkopp, 1988)Some rTMS studies have found rapid reductions in suicidality, a common issue among PCS patients. (*George*) Minimal side effects occurred; no one died of suicide within the 6 month follow-up.

Single sessions of TMS or rTMS do not carry the risk of significant magnetic field exposure since the total time is too short. (*Rossia*) One patient received 70 treatment sessions over 12 months, or 420,000 pulses, with no side effects. One 75-year old patient received 130 sessions over 26 months with a total number of 156,000 stimuli, while 7 patients received 60 sessions over 12 months with a total number of 72,000 stimuli. In another study (*Anderson*) healthy men were given 12,960 high intensity rTMS magnetic pulses a day for up to 3 days in 1 week. This equals 38,880 magnetic pulses over 1 week, one of the largest exposures of rTMS to date. Despite this intense treatment regimen, no significant side effects were seen. Doses of up to 12,960 pulses per day appear safe and tolerable in healthy young men.

Even in the setting of relapsing remitting multiple sclerosis comorbidity with TBI (*Ingram*) no patient showed evidence of relapse during follow-up of at least 8 months. The authors concluded

that magnetic brain stimulation was easy to perform, painless, and safe.

Some people also express a concern that EMFs might act as a cancer promoter. EMF exposure in rats with experimental brain glioma does not promote tumor growth (*Salford*).

Summary

Traumatic brain injury or concussion have been an ever present medical challenge for me as a doctor for over 40 years. The solutions to the problem today are little different than they were when I 1st learned about this problem in medical school. The biggest difference is that mild TBI, given the developing sophistication of medical knowledge, is now seen as a very important problem that needs to be dealt with sooner than later. In the past only more serious brain injuries took our attention, typically those that involved admissions to intensive care for coma. Now we know that mild TBI, especially recurrent mild TBI's leave very significant marks in the brain that result in major disability. The consequences of these TBI's of been brought to the fore recently with sports concussions.

Given that most of the therapies for mild to moderate TBI's are essentially adaptive, they help the body or person to cope or adapt to their disabilities, new approaches to managing this important condition are necessary. Modern evidence now suggests that even though somebody has recovered from their concussion, there are residual long-term effects in the brain. Other evidence indicates that the use of pulsed electromagnetic fields, of various kinds, early in the injury process helps to decrease one of the major aspects of the injury, which is inflammation in the brain. The inflammation then causes all sorts of short-circuiting of brain function eventually leading to the symptoms, not only those seen in short-term, but also long-term: headaches, dizziness, depression, anxiety, insomnia, etc., etc. Additional evidence now also tells us that pulsed electromagnetic field therapies can help with, not only the injury itself, but also many of the symptoms resulting from it. In other words, PEMFs are not only useful for symptom management in the person suffering from TBI/concussion, but also have the opportunity to actually heal the brain to reverse the long-term effects of brain damage.

Medical management today, especially with medication, is reserved for symptomatic management of the consequences of TBI, such as depression, headaches, memory issues, dizziness, etc. As such, therefore, medical management has very little role in helping people with TBI other than facilitating adaptation and symptom management.

So, while there is evidence that pulsed magnetic fields, which reach deep into the brain and help all layers and areas of the brain without risk or side effects, there is a need for growing the medical knowledge base about the use of PEMFs for concussion/TBI, including establishing protocols for different PEMF systems for intensity, time and duration of treatment, frequency of treatment, and frequencies that are best used. It appears that even very high intensity PEMFs used for extended periods of time produce virtually no adverse effects on the brain and may even decrease the risk of future cancer development and the development of Alzheimer's/dementia.

References

1. Anderson B, Mishory A, Nahas Z, Borckardt JJ, Yamanaka K, Rastogi K, George MS. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. J ECT. 2006 Mar;22(1):49-53.

2. Baker-Price L, Persinger MA. Intermittent burst-firing weak (1 microTesla) magnetic fields reduce psychometric depression in patients who sustained closed head injuries: a replication and electroencephalographic validation. Percept Mot Skills. 2003 Jun;96(3 Pt 1):965-74.

3. Baker-Price LA, Persinger MA. Weak, but complex pulsed magnetic fields may reduce depression following traumatic brain injury. Percept Mot Skills. 1996 Oct;83(2):491-8.

4. Bartko D, Turcáni P, Danisová J, et al. The effects of the pulsing magnetic field on the cerebral circulation, EEG power spectra and some properties of the blood. A preliminary data. J Bioelectr 7(1):131-132, 1988.

5. Bartnik-Olson BL, Harris NG, Shijo K, Sutton RL. Insights into the metabolic response to traumatic brain injury as revealed by (13)C NMR spectroscopy. Front Neuroenergetics. 2013 Oct 4;5:8.

6. Başar E, Schürmann M, Başar-Eroglu C, Karakaş S. Alpha oscillations in brain functioning: an integrative theory. Int J Psychophysiol. 1997 Jun;26(1-3):5-29.

7. Bell, G., A. Marino, A. Chesson and F. Struve (1991) Human sensitivity to weak magnetic fields. Lancet, 338: 1521—1522.

8. Berrigan L, Marshall S, McCullagh S, et al. Quality of clinical practice guidelines for persons who have sustained mild traumatic brain injury. Brain Inj. 2011;25(7-8):742-51.

9. Bharath RD, Munivenkatappa A, Gohel S, et al. Recovery of resting brain connectivity ensuing mild traumatic brain injury. Front Hum Neurosci. 2015 Sep 22;9:513.

10. Blackman CF. Stimulation of brain tissue in vitro by extremely low frequency, low intensity, sinusoidal electromagnetic fields. Prog Clin Biol Res 257:107-117. Electromagnetic Fields and Neurobehavioral Function, M. E. O'Connor and R. H. Lovely, eds., New York: Alan R. Liss, Inc. 1988.

11. Bonnì S, Mastropasqua C, Bozzali M, et al. Theta burst stimulation improves visuo-spatial attention in a patient with traumatic brain injury. Neurol Sci. 2013 Nov;34(11):2053-6.

12. Choe MC, Giza CC. Diagnosis and management of acute concussion. Semin Neurol. 2015 Feb;35(1):29-41.

13. Clark VP, Parasuraman R. Neuroenhancement: enhancing brain and mind in health and in disease. Neuroimage. 2014 Jan 15;85 Pt 3:889-94.

14. Cosentino G, Giglia G, Palermo A, et al. A case of post-traumatic complex auditory hallucinosis treated with rTMS. Neurocase. 2010 Jun;16(3):267-72.

15. Del Percio C, Marzano N, Tilgher S, Fiore A, Di Ciolo E, Aschieri P, Lino A, Toràn G, Babiloni C, Eusebi F. Pre-stimulus alpha rhythms are correlated with post-stimulus sensorimotor performance in athletes and non-athletes: a high-resolution EEG study. Clin Neurophysiol. 2007 Aug;118(8):1711-20.

16. Diamond MC, Tenforde TS, Liburdy RP, et al. The influence of ultrahigh magnetic fields on cerebral cortical morphological development: a preliminary study (meeting abstract). Bioelectromagnetics Society, 11th Annual Meeting, 18-22 June, Tucson, AZ, Abstract No. P-1-20, p. 62-63, 1989.

17. Dowman R, Wolpaw JR, Seegal RF, Satya-Murti S. Chronic exposure of primates to 60-Hz electric and magnetic fields: III. Neurophysiologic effects. Bioelectromagnetics. 1989;10(3):303-17.

18. Esty ML and Nelson D. Neurotherapy of TBI/PTSD in OEF/OIF Veterans. The Journal of Neuropsychiatry and Clinical Neurosciences, 21:221-223, 2009.

19. Gavalas RJ, Walter DO, Hamer J, Adey WR. Effect of low-level, low-frequency electric fields on EEG and behavior in Macaca nemestrina. Brain Res 1970; 18 (3): 491 – 501.

20. George MS, Raman R, Benedek DM, et al. A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul. 2014 May-Jun;7(3):421-31.

21. Goodwin T. Physiological and molecular genetic effects of time-varying electromagnetic fields on human neuronal cells. NASA Johnson Space Center, Houston, TX, United States. NASA/TP-2003-212054.

22. Grunner O. Cerebral use of a pulsating magnetic field in neuropsychiatry patients with long-term headache. EEG EMG Z Elektroenzephalogr Verwandte Geb (1985) Dec;16(4):227-230. the

23. Herrold AA, Kletzel SL, Harton BC, et al. Transcranial magnetic stimulation: potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. Neural Regen Res. 2014 Oct 1;9(19):1712-30.

24. Hoffer ME. Mild traumatic brain injury: neurosensory effects. Curr Opin Neurol. 2015 Feb;28(1):74-7.

25. Ingram DA, Thompson AJ, Swash M. Central motor conduction in multiple sclerosis: evaluation of abnormalities revealed by transcutaneous magnetic stimulation of the brain. J Neurol Neurosurg Psychiatry 51(4):487-494, 1988.

26. Jin Y, Phillips B. A pilot study of the use of EEG-based synchronized Transcranial Magnetic Stimulation (sTMS) for treatment of Major Depression. BMC Psychiatry. 2014 Jan 18;14:13.

27. Koski L, Kolivakis T, Yu C, et al. Noninvasive brain stimulation for persistent postconcussion symptoms in mild traumatic brain injury. J Neurotrauma. 2015 Jan 1;32(1):38-44.

28. Lee J, Choi BH, Oh E, et al. Treatment of Alzheimer's Disease with Repetitive Transcranial Magnetic Stimulation Combined with Cognitive Training: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. J Clin Neurol. 2015 Sep 11.

29. Leuchter AF, Cook IA, Feifel D, et al. Efficacy and Safety of Low-field Synchronized Transcranial Magnetic Stimulation (sTMS) for Treatment of Major Depression. Brain Stimul. 2015;8(4):787-94.

30. Leuchter AF, Cook IA, Jin Y, Phillips B. The relationship between brain oscillatory activity and therapeutic effectiveness of transcranial magnetic stimulation in the treatment of major depressive disorder. Front Hum Neurosci. 2013 Feb 26;7:37.

31. Leuchter AF, Hunter AM, Krantz DE, Cook IA. Rhythms and blues: modulation of oscillatory synchrony and the mechanism of action of antidepressant treatments. Ann N Y Acad Sci. 2015 May;1344:78-91.

32. Leung A, Fallah A, Shukla S, Lin L, Tsia A, Song D, Polston G, Lee R. rTMS in Alleviating Mild TBI Related Headaches - A Case Series. Pain Physician. 2016 Feb;19(2):E347-54.

33. Liao X, Li G, Wang A, et al. Repetitive Transcranial Magnetic Stimulation as an Alternative Therapy for Cognitive Impairment in Alzheimer's Disease: A Meta-Analysis. J Alzheimers Dis. 2015 Sep 9;48(2):463-72.

34. Ling H, Hardy J, Zetterberg H. Neurological consequences of traumatic brain injuries in sports.

Mol Cell Neurosci. 2015 May;66(Pt B):114-22.

35. Louise-Bender Pape T, Rosenow J, Lewis G, et al. Repetitive transcranial magnetic stimulation-associated neurobehavioral gains during coma recovery. Brain Stimul. 2009 Jan;2(1):22-35.

36. Lustenberger C, Boyle MR, Foulser AA, Mellin JM, Fröhlich F. Functional role of frontal alpha oscillations in creativity. Cortex. (2015) Jun;67:74-82.

37. MacFarlane MP, Glenn TC. Neurochemical cascade of concussion. Brain Inj. 2015;29(2):139-53.

38. Marshall S, Bayley M, McCullagh S, et al. Clinical practice guidelines for mild traumatic brain injury and persistent symptoms. Can Fam Physician. 2012 Mar;58(3):257-67, e128-40.

39. Meehan WP 3rd. Medical therapies for concussion. Clin Sports Med. 2011 Jan;30(1):115-24, ix.

40. Mez J, Solomon TM, Daneshvar DH, et al. Pathologically Confirmed Chronic Traumatic Encephalopathy in a 25-Year-Old Former College Football Player. JAMA Neurol. 2016 Jan 4:1-3.

41. Nelson DV, and Esty ML. Neurotherapy for pain in veterans with trauma spectrum disorders. The Journal of Pain 10:S18, 2009.

42. Nelson DV, Esty ML. Neurotherapy for chronic headache following traumatic brain injury. Mil Med Res. 2015 Aug 31;2:22.

43. Nelson, D and Esty, ML. Neurotherapy for Chronic TBI/PTSD Symptoms in Vietnam Veterans. The Journal of Head Trauma Rehabilitation. 2009 (24)5, 403.

44. Niedermeyer, E. (1999) The Normal EEG of the Waking Adult. Electroencephalography. Lippincott Williams y Wilkins, Baltimore.

45. Nielson DM, McKnight CA, Patel RN, et al. Preliminary guidelines for safe and effective use of repetitive transcranial magnetic stimulation in moderate to severe traumatic brain injury. Arch Phys Med Rehabil. 2015 Apr;96(4 Suppl):S138-44.

46. Ontario Neurotrauma Foundation. Guidelines for concussion/mild traumatic brain injury and persistent symptoms. 2nd edition. 2013. For adults.

47. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007 Dec 1;62(11):1208-16.

48. Ossenkopp KP, Cain DP. Inhibitory effects of acute exposure to low-intensity 60-hz magnetic fields on electrically kindled seizures in rats. Brain Res 442(2):255-260, 1988.

49. Ossenkopp KP, Kavaliers M. Clinical and applied aspects of magnetic field exposure: a possible role for the endogenous opioid system. J Bioelectr 7(2):189-208, 1989.

50. Pape TL, Rosenow J, Lewis G. Transcranial magnetic stimulation: a possible treatment for TBI. J Head Trauma Rehabil. 2006 Sep-Oct;21(5):437-51.

51. Persinger MA, Saroka KS. Comparable proportions of classes of experiences and intracerebral consequences for surgical stimulation and external application of weak magnetic field patterns: implications for converging effects in complex partial seizures. Epilepsy Behav. 2013 Apr;27(1):220-4.

52. Peskind ER, Brody D, Cernak I, et al. Military- and sports-related mild traumatic brain injury: clinical presentation, management, and long-term consequences. J Clin Psychiatry (2013)74: 180–188.

53. Politis MJ, Zanakis MF. Treatment of the damaged rat hippocampus with a locally applied electric field. Exp Brain Res 71(1):223-226, 1988.

54. Raji CA, Tarzwell R, Pavel D, et al. Clinical utility of SPECT neuroimaging in the diagnosis and treatment of traumatic brain injury: a systematic review. PLoS One. 2014 Mar 19;9(3):e91088.

55. Rasouli J, Lekhraj R, White NM, Flamm ES, Pilla AA, Strauch B, Casper D. Attenuation of interleukin-1beta by pulsed electromagnetic fields after traumatic brain injury. Neurosci Lett. 2012 Jun 21;519(1):4-8.

56. Reti IM, Schwarz N, Bower A, et al. Transcranial magnetic stimulation: A potential new treatment for depression associated with traumatic brain injury. Brain Inj. 2015;29(7-8):789-97.

57. Rohan ML, Yamamoto RT, Ravichandran CT, et al. Rapid mood-elevating effects of low field magnetic stimulation in depression. Biol Psychiatry. 2014 Aug 1;76(3):186-93.

58. Rossia S, Hallett M, Rossini, PM, Pascual-Leone A. The Safety of TMS Consensus Group1. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009 December ; 120(12): 2008–2039.

59. Salam MT, Kassiri H, Genov R, et al. Rapid brief feedback intracerebral stimulation based on real-time desynchronization detection preceding seizures stops the generation of convulsive paroxysms. Epilepsia. 2015 Aug;56(8):1227-38.

60. Salford LG, Brun A, Eberhardt JL, Persson BRR. Development of rat brain tumours during exposure to continuous and pulsed 915 MHz electromagnetic radiation (meeting abstract). First World Congress for Electricity and Magnetism in Biology and Medicine, 14-19 June, Lake Buena Vista, FL, Abstract No. I-1, p. 27-28, 1992.

61. Schoenberger NE, Shif SC, Esty ML, et al. Flexyx Neurotherapy System in the treatment of traumatic brain injury: an initial evaluation. J Head Trauma Rehabil. 2001 Jun;16(3):260-74.

62. Seegal RF, Wolpaw JR, Dowman R. Chronic exposure of primates to 60-Hz electric and magnetic fields: II. Neurochemical effects. Bioelectromagnetics. 1989;10(3):289-301.

63. Sieron A, Labus L, Nowak P, Cieslar G, Brus H, Durczok A, Zagzil T, Kostrzewa RM, Brus R. Alternating extremely low frequency magnetic field increases turnover of dopamine and serotonin in rat frontal cortex. Bioelectromagnetics 25:426– 430, 2004.

64. Simpson G, Tate R. Suicidality in people surviving a traumatic brain injury: prevalence, risk factors and implications for clinical management. Brain Inj. 2007 Dec;21(13-14):1335-51.

65. Sokhadze EM, El-Baz AS, Tasman A, et al. Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: an exploratory study. Appl Psychophysiol Biofeedback. 2014 Dec;39(3-4):237-57.

66. Tang HY, Vitiello MV, Perlis M, Riegel B. Open-loop neurofeedback audiovisual stimulation: a pilot study of its potential for sleep induction in older adults. Appl Psychophysiol Biofeedback. 2015 Sep;40(3):183-8.

67. VA/DoD Clinical Practice Guideline for Management of Concussion/Mild Traumatic Brain Injury. Management of Concussion/mTBI Working Group. J Rehabil Res Dev. 2009;46(6):CP1-68.

68. Warden DL, Bleiberg J, Cameron KL, et al. Persistent prolongation of simple reaction time in sports concussion. Neurology. 2001 Aug 14;57(3):524-6.

69. Wever, R.A. (1987) The electromagnetic environment and the circadian rhythms of human subjects. In: M. Grandolfo, SM. Michaelson and A. Rindi (Eds.), Biological Effects and Dosimetry of Static and ELF Electromagnetic Fields, Plenum Press, New York, NY.

70. Wolpaw JR, Seegal RF, Dowman R. Chronic exposure of primates to 60-Hz electric and magnetic fields: I. Exposure system and measurements of general health and performance. Bioelectromagnetics. 1989;10(3):277-88.

71. Yuh EL, Mukherjee P, Lingsma HF, et al. (2013) Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. Ann Neurol 73: 224–235.

72. Zecca,L, Margonato V, Esposti G, et al. Brain transmitters in rats exposed to 50 hz pulsed magnetic fields. (meeting abstract) J Bioelectr 8(2):269, 1989. International Symposium in Honor of Luigi Galvani, 14-16, April, Bologna, Italy.