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Pilot Clinical Data Showing Positive Therapeutic Outcomes for Concussion: Personalized repetitive magnetic stimulation (PrTMS®) guided by EEG spectra

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Abstract: There are no FDA-approved treatments for the chronic sequelae of concussion. Repetitive magnetic transcranial stimulation (rTMS) has been explored as a therapy but outcomes have been inconsistent. To address this we developed a personalized rTMS (PrTMS) protocol involving continual rTMS stimulus frequency adjustment and progressive activation of multiple cortical sites, guided by spectral electroencephalogram (EEG)-based analyses and psychological questionnaires. We acquired pilot clinical data for 241 symptomatic brain concussion patients who underwent the PrTMS protocol over an approximately 6 week period. The PrTMS protocol used a proprietary EEG spectral frequency algorithm to define an initial stimulation frequency based on an anteriorly graded projection of the measured occipital alpha center peak, which was then used to interpolate and adjust regional stimulation frequency according to weekly EEG spectral acquisitions. PrTMS improved concussion indices and normalized the cortical alpha band center frequency and peak EEG amplitude. This potentially reflected changed neurotransmitter, cognitive, and perceptual status. PrTMS may be a promising treatment choice for patients with persistent concussion symptoms. Moreover, these early findings offer support for prospective research on PrTMS in concussion and exploration of the spectral EEG as a concussion biomarker, with the ultimate goal of confirming these findings and determining optimal PrTMS parameters and treatment duration.

Keywords: repetitive transcranial magnetic stimulation (rTMS); concussion; electroencephalogram (EEG); power spectrum; Rivermead Post Concussion Symptoms Questionnaire (RPQ); regression

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1. Introduction

Mild traumatic brain injury (mTBI) is generally referred to as concussion, and is chiefly caused by motor vehicle accidents, falls, assaults, and sports related impacts [1, 2]. Concussion is widespread and in a significant proportion of affected patients it is disabling [2-5]. There are few treatment options and the long-held perspective that mild concussion resolves relatively rapidly and without sequelae is being questioned [6-8]. Reports have related higher rates of depression and dementia with a history of concussion [9-11]. The need for effective treatments has prompted the use of repetitive transcranial magnetic stimulation (rTMS) which has shown beneficial activity in concussion, although results have been mixed [2]. We have developed a comparatively dynamic form of rTMS, called personalized rTMS (PrTMS), which methodologically aligns with emerging mechanistic data that has provided greater insight into the pathophysiology of concussion [12, 13]. Based on the previous application of standard (non-personalized) rTMS for mild traumatic brain injury, despite mixed results, we decided to perform this study utilizing our novel personalized approach in a large number of mTBI patients (n=241) with persistent concussion symptoms. A review by Mollica and colleagues (2021) showed that rTMS concussion studies have been small in scope, ranging between 6 and 29 subjects [2].

While much remains to be learned about the neurophysiology and neurobiology of concussion, the ability of rTMS to entrain and synchronize neurons has attracted attention for the re-establishment of normal, distributed alpha oscillatory rhythms. Inflammatory activity may be reduced by rTMS, while activation of neurotransmitters to rebalance signaling, reduce depression symptoms, and induce plasticity for CNS repair may be induced by rTMS [14-17]. The review by Mollica et al, (2021) was a metanalysis of 342 studies of rTMS in mTBI [2]. The authors concluded that in sham-controlled studies, 1 to 4 weeks of rTMS showed benefit for post concussive headache and depression, but, importantly, not all studies showed improvement.

There are two key considerations that may highlight the applicability of PrTMS for concussion treatment. First, our experience with spectral EEG with hundreds of concussion patients often demonstrates diffuse cortical frequency irregularities, extending from the orbital frontal cortex posterior to the visual cortices. Others have noted a large variability and distribution of brain wave frequencies in concussion [12]. Individualized rTMS treatment regimens have also been proposed by others [8]. We hypothesized that treatment delivery to all or most of these cortical locations would be necessary to re-establish oscillatory synchrony. Standard rTMS is unable to accomplish this, due to increased treatment intensity (amplitude) at or above the motor neuron threshold. Direct treatment of the motor-sensory strip, for example, would cause seizure. Lower amplitude stimulation with PrTMS allows direct stimulation of the motor-sensory strip and other sensitive cortical locations with virtually no risk of overstimulation causing seizure. Moreover, standard rTMS typically involves delivery of a fixed 10.0 Hz treatment frequency. Based on the literature we believed that in many patients, 10.0 Hz may not be the correct frequency, and may in fact add to a destructive stimulatory pattern, versus a preferred constructive pattern. Additionally, the reliability of traditional cognitive assessment tools and imaging has increasingly been questioned, and there is an expanding focus on non-subjective assessments that are based on the spectral EEG to evaluate post-concussive brain alterations that are otherwise difficult to identify [18].

Based on the foregoing, PrTMS may offer a solution, as spectral EEG analyses and not just psychological self-reported questionnaires, are used to guide frequent adjustments of stimulus frequency, along with the identification and treatment of multiple, affected cortical sites. The oscillatory activity of the brain cortex has been addressed via the EEG 1/fa power spectrum, an emerging analytical approach initially described in detail by Voytek et al (2015), that aligned with early publications addressing the importance of synchronous brain oscillations, and that has since expanded [19-22]. Changes in the 1/fa

aperiodic component *within* individuals may reflect shifts in dominant cortical neurotransmitters and changed cognitive status and perceptual encoding, and could advance as an independent biomarker of neuropsychiatric disorders [19, 23].

Here we report pilot clinical data obtained with mTBI patients who had persistent symptoms of concussion and were seeking effective treatment options. We treated these individuals with PrTMS, and the data suggested that PrTMS was associated with a considerable improvement in symptoms. We present EEG alpha band center frequency and $1/f^a$ spectral power spectrum analyses for concussion patients, which exhibited changes after PrTMS therapy. Despite the difficulty and rarity of incorporating control groups in concussion studies, the favorable outcomes and their EEG correlates presented here, may warrant more comprehensive prospective studies of PrTMS for concussion. Importantly, $1/f^a$ based analyses of the spectral EEG may serve as a much needed and readily acquired biomarker in concussion.

2. Methods

2.1. Subjects

Males and females came to our clinic indicating that they had persistent concussion symptoms (male/female ratio = 1.4:1) and were screened for concussion using either the self-reported Median Concussion Symptom Inventory (CSI) or the Rivermead Post Concussion Symptoms Questionnaire (RPQ). The patients were of all ethnicities, the average age was 38 years, and 241 patients received 6 weeks of PrTMS treatment. Patients and/or their families sought out our clinic because of persistent concussion symptoms and the desire for an effective treatment option. The rTMS eligibility criteria defined by Rossi et al (2009), McClintock et al (2018), and Rossi et al (2021) were used for patient screening [24-26]. Patients were briefed on the treatment procedures and they provided informed medical consent for PrTMS. Moreover, before our retrospective review, institutional review board (IRB) approval was obtained: WCG IRB Study number 1254094; IRB tracking number 20190239; Title: A Retrospective Review of Personalized Repetitive Magnetic Stimulation (PrTMS®). Patients were encouraged to continue their standard psychotherapy and/or medication management during the course of PrTMS treatment. The duration of treatment was open ended and was predicated on patient preferences in the context of perceived and quantifiable progress.

2.2. Treatment Schedule

PrTMS was administered once daily for five days a week as shown in Figure 1, and the duration of treatment was typically 6 to 8 weeks or 30-40 treatments. Importantly, the electroencephalogram (EEG) was acquired regularly for each patient as this neurophysiological measure represents an independent, non-subjective treatment response indicator [18]. Hence, the EEG was obtained before PrTMS commenced, and on the first day of each week of PrTMS. Power spectrum analysis of all 19 leads and a single heart lead, were then rendered into a display, and plotted in time series along the "x" axis from 2-20 Hz. A proprietary frequency algorithm (*PeakLogic, Inc*. San Diego) defined an initial stimulation frequency which was a result of a mathematical summary of the aggregate alpha center peak frequency, minus the "noise factor" introduced into the rendering from the destructive wave interference(s) created by all other measured waves. This algorithm was used to interpolate and adjust regional stimulation frequency, amplitude, length of train, intertrain interval, and number of treatments according to weekly EEG spectral acquisitions. In addition, concussion symptoms and sleep quality in a small subset of patients were assessed weekly using the self-report Rivermead Concussion Symptom Inventory (CSI), and the Sleep Condition Indicator (SCI) questionnaire, respectively. Patients had follow-up questionnaire and EEG visits at 11 weeks and a few patients (n = 13) returned at 24

weeks. Patient activities, sleep, sports, etc., were not monitored after they finished the 6 week course of PrTMS.

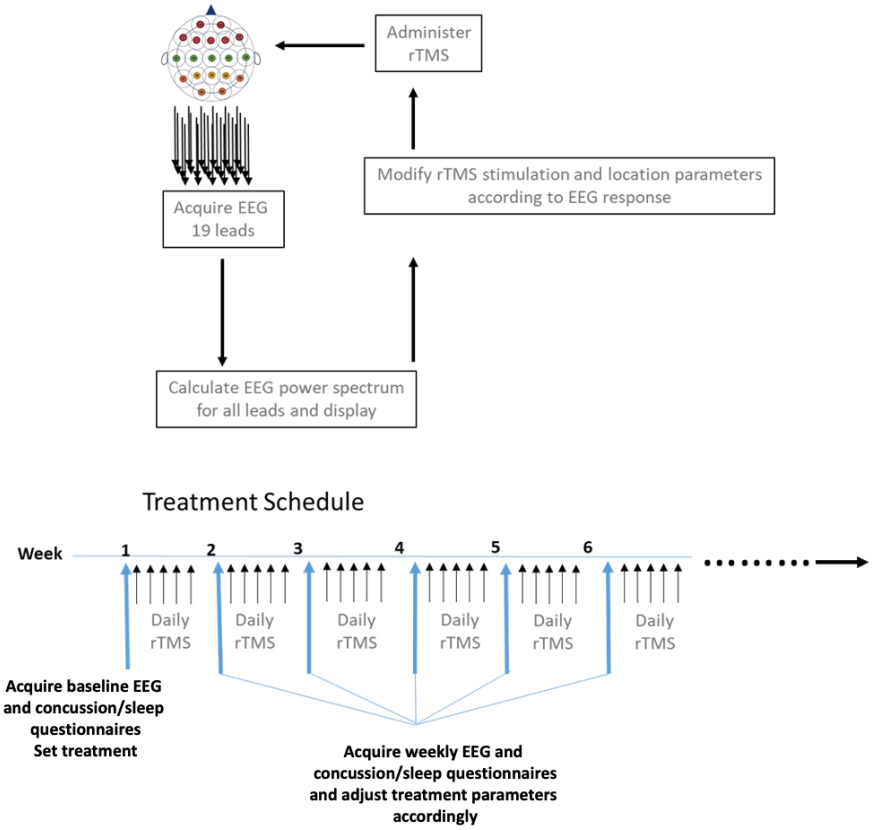

Figure 1. PrTMS treatment plan and schedule. PrTMS was adjusted weekly in terms of stimulation amplitude, frequency, intertrain interval, length of treatment train, and cortical locations (a minimum of 3 and maximum of 5 locations) treated each day. The EEG was acquired weekly and analyzed spectrally, and concussion questionnaires and sleep questionnaires were also administered every week.

2.3. EEG Data Acquisition

EEG recordings were acquired before PrTMS and just before every sixth treatment as long as PrTMS continued. The EEG was recorded from awake, eyes closed, seated subjects using a 19-lead high impedance dry electrode EEG headset (Cognionics [CGX] Inc., San Diego CA). Data filtering was avoided and technically flawed recordings were removed by an experienced observer. A four-minute EEG time epoch was transformed via Welch's Fast Fourier Transform (FFT) using a custom Python program, to produce a 2-20 Hz power spectrum with 0.1 Hz resolution.

2.4. Personalized Repetitive Transcranial Magnetic Stimulation (PrTMS)

PrTMS was delivered by a qualified, trained rTMS technician using a MagVenture MagPro R30 transcranial stimulator and B-65 head transducer. Patients were seated in a quiet room with the eyes closed and without sedation. Magnetic field intensity was gradually increased over the course of treatment. Stimulation intensity was 25-60% of the typical resting motor threshold (MT) in most patients, and the stimulus frequency range was 8-13 Hz, with magnetic pulses delivered in 10-15 second trains. Intertrain intervals began at 30 seconds, and gradually decreased to 10 seconds. During each treatment session, the motor-sensory strip and subsequent prefrontal and frontal regions were treated in succes-

sion. Clinical personnel evaluated patients daily for adverse events (AEs) including headache, scalp pain, cognitive deficits, seizures, observed or volunteered problems, complaints, physical signs and symptoms, medical conditions that were not previously present, and previous medical conditions that worsened.

2.5. Data Analysis and Statistical Methods

2.5.1. Rivermead and Sleep Quality Scores

The primary endpoint was the reduction in symptoms measured by concussion questionnaires, including the Concussion Symptom Inventory (CSI) and the Rivermead Concussion Index (RPQ), and the sleep quality questionnaire (Sleep Condition Indicator – SCI). These were the only continuous variables, acquired weekly from baseline (pretreatment) to final treatment. The mean change from baseline (CFB) data were tested using a two-sided t-test (α=0.05 level of significance). There was no adjustment for multiplicity, and missing data imputation was not implemented.

2.5.2. EEG Spectral Analyses

The dominant alpha peak (center) frequency was determined for all EEG leads, averaged for each cortical region, and the amplitude of the alpha band (8-13 Hz) spectral center frequency was identified in each EEG lead during for each week of treatment. The $1/f^{\alpha}$ aperiodic spectral component was determined by averaging the 2-20 Hz power spectrum amplitude from the 7 leads in the frontal cortex, plotting log power versus log frequency, and then calculating the robust regression line and its slope, treating periodic oscillatory components as outliers. The amplitude of the alpha (slope) from zero was then determined.

3. Results

3.1. Concussion Symptom Inventory (CSI)

Importantly, while this paper reports the outcomes obtained from medical treatment, and is not based on a prospective study, the patients all had persistent concussion symptoms for which they sought a viable treatment option. The Concussion Symptom Inventory (CSI) in 56 patients of all ages detected a significant decline in concussion symptoms after PrTMS was initiated as shown in Figures 2a and 2b, from a mean of 33.5 to 10.5 (paired t-test, $p<0.0001$). The mean number of treatment days in this group was 9 and ranged between 6 and 19, suggesting that patients responded rapidly, and that they were indeed responding to treatment. Only 2 of 56 patients failed to respond positively. While a distinct cutoff score has not been defined for the CSI, patients exhibited marked improvement with mean scores dropping by almost 70%.

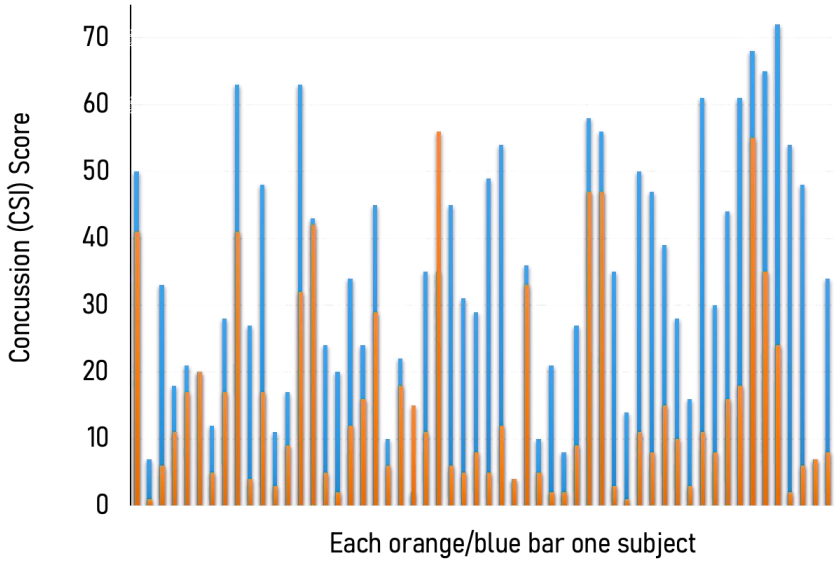

Figure 2a Consistent reduction in concussion symptoms inventory (CSI) across a cohort of 56 individual patients. Each orange and blue combined bar is one subject, and the blue portion indicates the CSI before PrTMS, while the orange segment denotes the CSI score after PrTMS. A paired 2-tailed parametric t-test compared before vs after scores ($p<0.0001$). The average number of treatments was 9 and the range was 6 to 19.

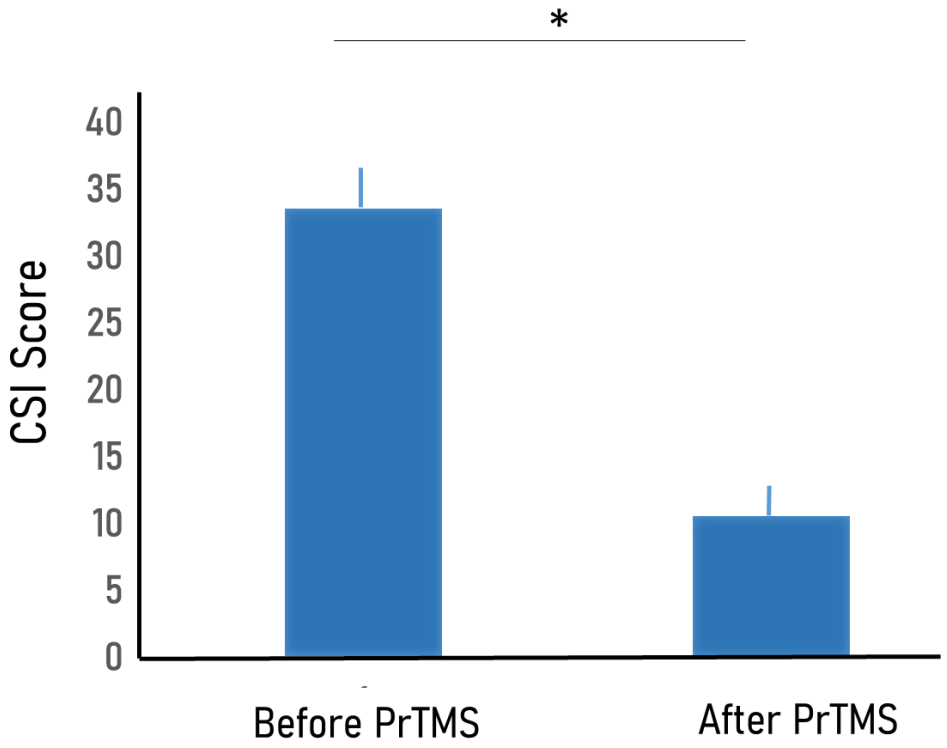

Figure 2b. Median concussion symptom inventory (CSI) in a cohort of 56 patients of all ages before and after PrTMS. Average number of treatments is 9 and the range was 6 to19. Mean before and after PrTMS CSI scores are shown for all 56 patients and SEMS are indicated on the bars. A parametric, 2-tailed paired t-test compared before versus after PrTMS for all subjects (*$p<0.0001$).

3.2. Rivermead Concussion Questionnaire Scores

Initially the average Rivermead concussion questionnaire (RPQ) score for 185 patients was 26.2 (SE 1.0) which was above the threshold of 16 for concussion according to Thompson et al (2020). After 6 weeks of treatment the mean score was reduced to 18.2 (SE 0.83, n=185), and at the 11 and 24 week follow ups the mean scores were 16 (SE 3.1, n=61), and 16.25 (SE 1.97, n= 8), respectively, as depicted in **Figure 3**. A parametric two tailed t-test indicated that these pre- versus post-treatment differences from baseline to 6 weeks and the 11 week ($p<0.0001$) follow-up were significant. It should be noted in this context that while the total Rivermead score indicates the severity of the post concussive syndrome, a broadly accepted definitive clinical cut off score has been not been established. Nonetheless, the postulated threshold is 16 for clinically significant concussion symptoms, according to work by Thompson and co-workers (2016).

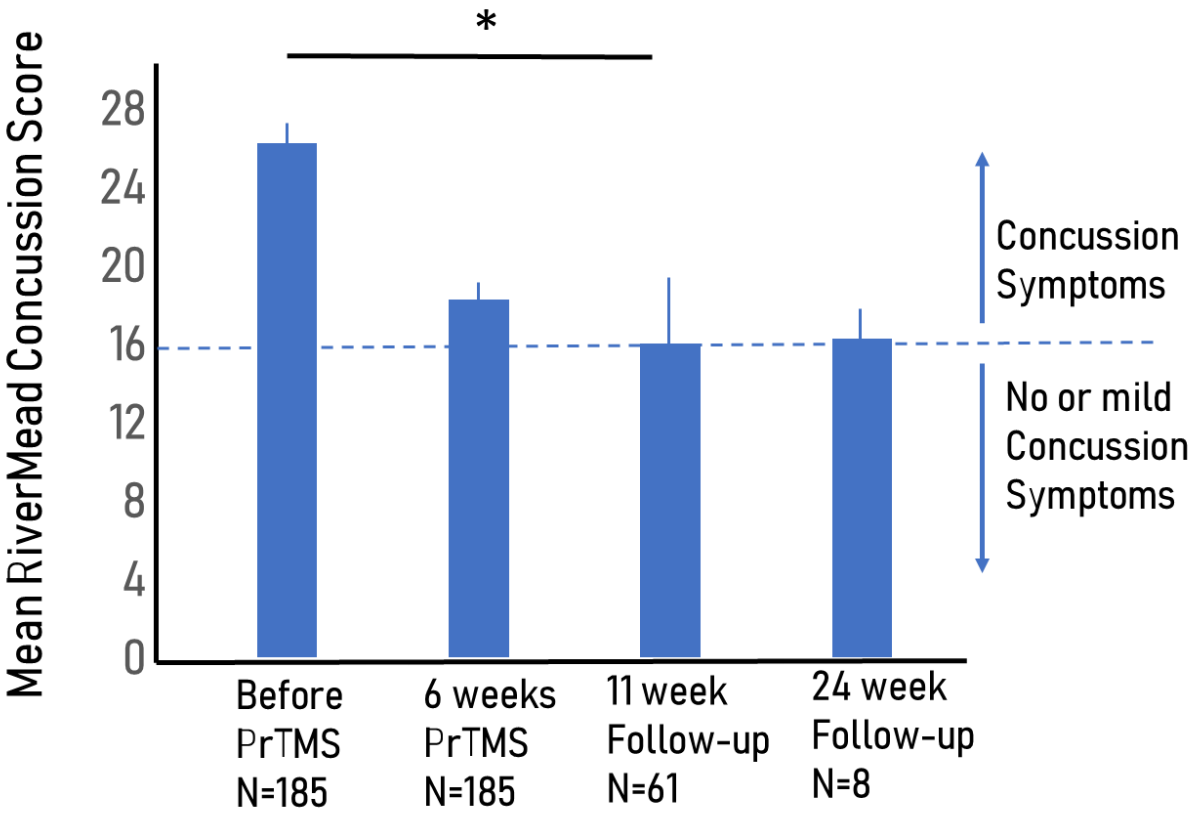

Figure 3. Reduction in Rivermead Concussion Inventory scores for 185 patients of all ages suffering from persistent concussion symptoms before and after PrTMS. The bar graph shows the concussion score before treatment, at 6 weeks of treatment, and at the 11 and 24 week follow ups. SEMs are indicated and the score threshold of 16 which divides concussion versus no concussion is shown by the dashed line. The average score before PrTMS was 26.2 and at 6 weeks was 18.2, at 11 weeks was 16, and at 24 weeks was 16.25. All of the after PrTMS scores indicate very mild or no concussion symptoms (*$p<0.0001$ for weeks 6 and 11, paired 2-=tailed t-test). Note that at the 24 week mean score was approximately the same as at 6 and 11 weeks, but was not statistically significantly different from pre-treatment.

3.3. Sleep Quality and Insomnia Scores

Patients treated with PrTMS reported at least some sleep improvement according to the self-reported Sleep Condition Indicator (SCI) (**Figure 4**). The mean sleep quality score improved (higher score shows improvement) from 12.4 to 18.7 after 6 weeks of PrTMS ($p=0.0034$, n=61). This post treatment value is above the putative CSI cutoff of 16, which

according to the definition of Espie et al (2014) correctly identifies 89% of subjects as having probable insomnia disorder, and 82% of subjects as not having insomnia disorder.

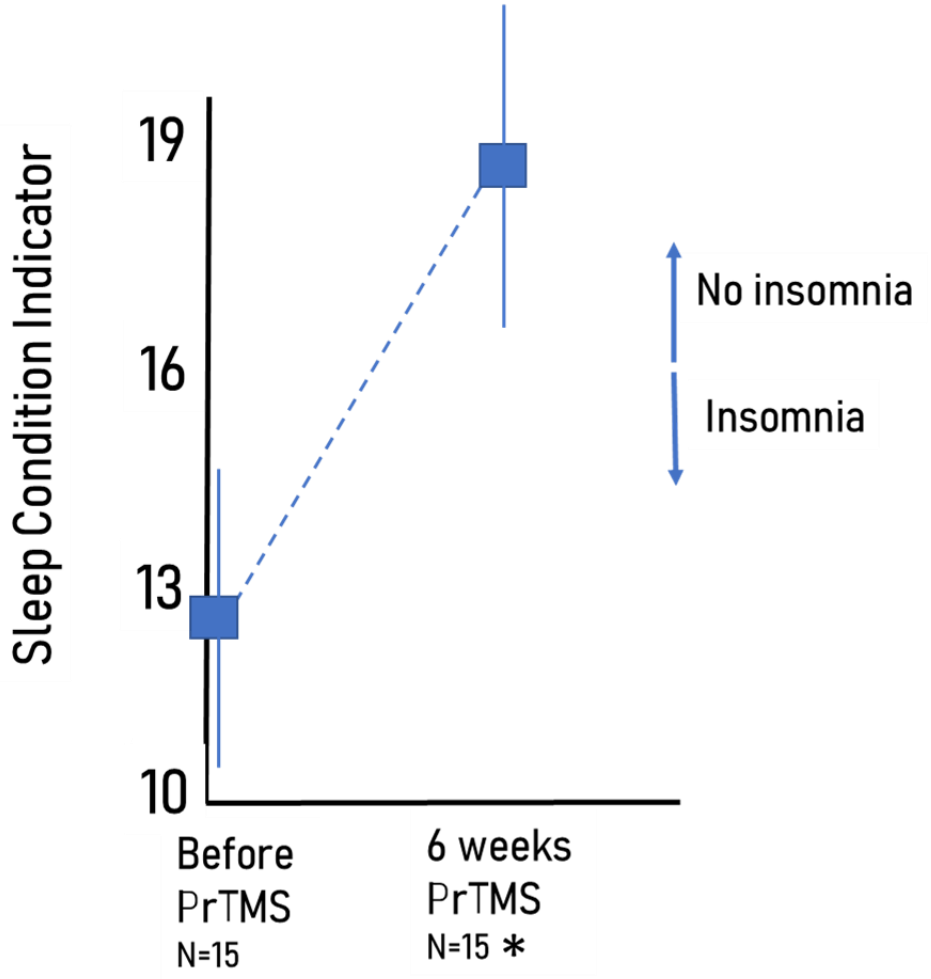

Figure 4. Average increase in the Sleep Condition Indicator (SCI) score. The average improvement was from 12.4 before treatment to 18.7 at 6 weeks (SEM shown, $p<0.0034$, paired t-test). When the SCI is less than or equal to 16, which is shown on the graph by the dashed line, the patient has probable insomnia. There were 15 subjects.

3.4. EEG Alpha Bband Center Frequency and 1/f^{a} Spectral Regression

The EEG potentially may provide a useful, non-subjective index of concussion patient status and response to treatment. While questionnaires may contain some subjective bias, neurophysiological measures such as the EEG are likely independent of the subject's personal perceptions and are objective. We observed that at the 6th EEG, i.e., after 5 weeks of PrTMS the alpha band center frequency declined for all brain regions, shown in **Figure 5a**. A paired t-test showed that the reduction for all brain regions together was significant ($p=0.0035$).

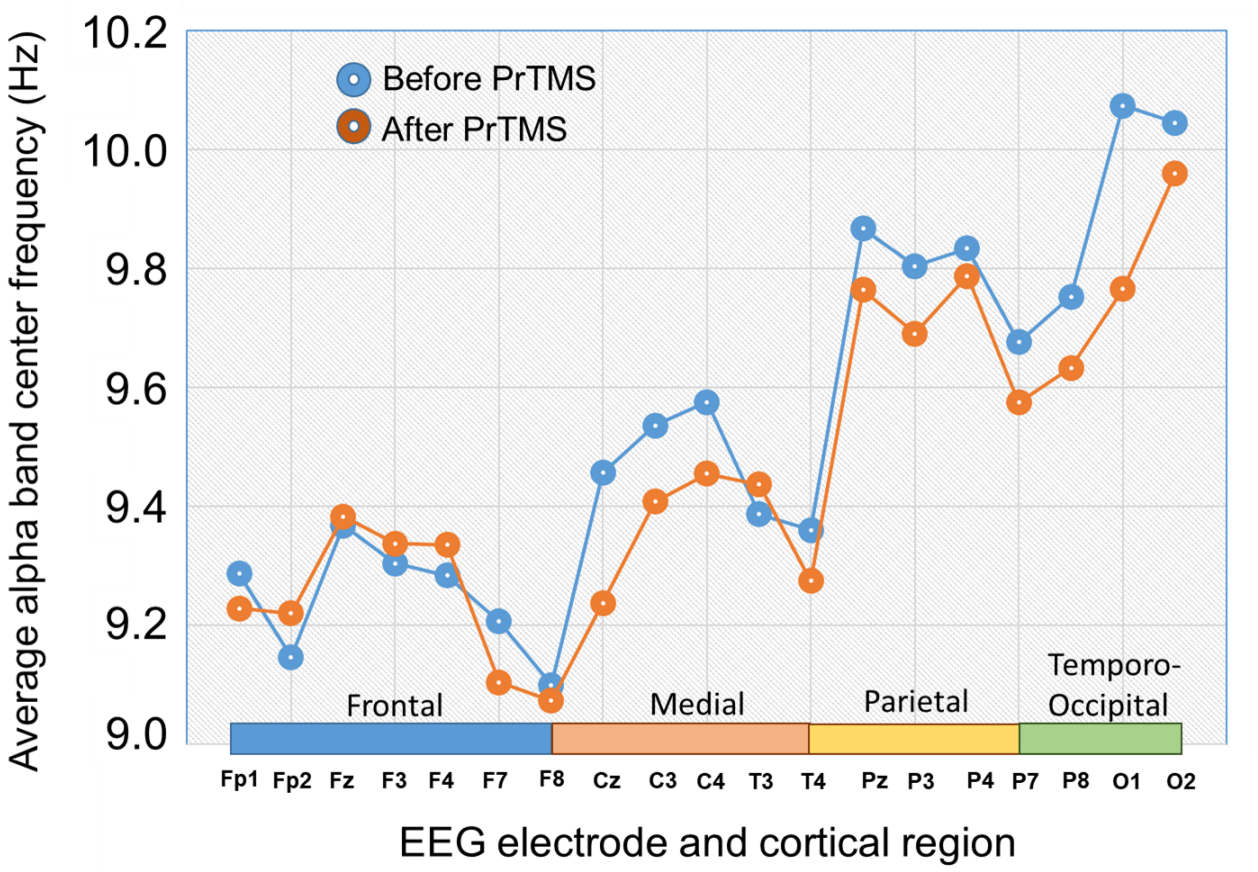

Figure 5a. Alpha peak center frequencies at 6 weeks after PrTMS. The alpha band peak center frequencies for all brain regions (BR1=frontal, BR2=central, BR3=parietal, BR4=occipital) in subjects suffering from persistent concussion symptoms. A repeated measures ANOVA indicated that the post PrTMS alpha frequency change although relatively small, was significant.

The alpha peak portion the EEG power spectrum for all 4 brain regions in the subjects assumed its expected relative amplitude and shape after 6 weeks PrTMS (**Figure 5b)**. By 6 weeks the alpha band spectra appear more synchronous, and at the 11 and 24 week follow ups they are still more synchronous than before treatment, but appear less aligned than at 6 weeks. At the 24-week follow-up the EEG alpha peak amplitude was much reduced and the center frequency declined, although there were only 13 patients in this group. The relative area of the alpha peak compared to pretreatment was reduced at 6 weeks of PrTMS, while at the 11 and 24 week follow ups compared to respective pretreatment values, it was greater. **(Figure 5c)**.

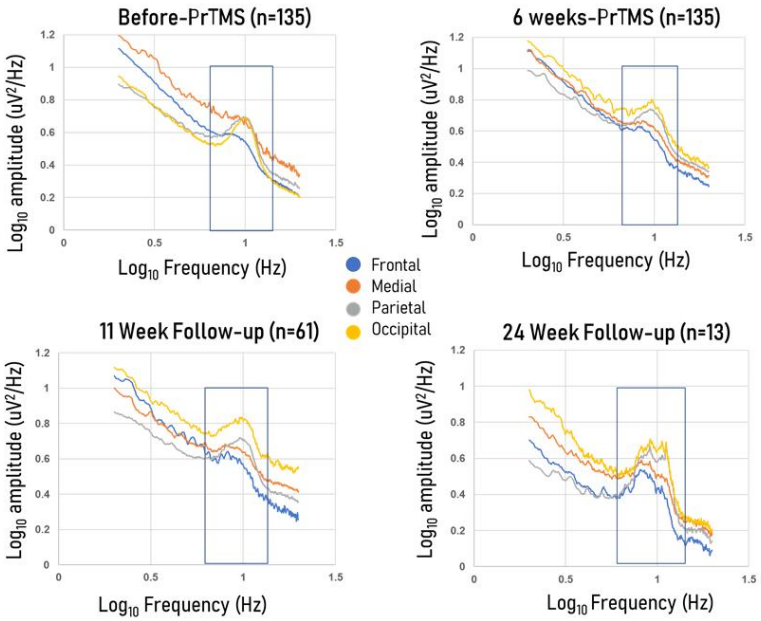

Figure 5b Logarithmic plots of averaged EEG power spectra for each brain region at each timepoint. The four panels show mean log-log plots of frontal, medial, parietal, and occipital EEG power spectra for all subjects suffering from persistent concussion symptoms. The time points are, before PrTMS, at 6 weeks (n=135) of PrTMS, and at the 11-week (n=61) and 24 week (n=13) follow-ups. Note the disorganized appearance of the power spectrum before PrTMS both outside and within the alpha peak (box outline). After 6 weeks of PrTMS the expected posterior-anterior amplitude gradient, i.e., Occipital>Parietal>Central>Frontal, for the alpha peak was re-established, (highlighted by the box outline) and the brain region spectra exhibited close overall alignment. The 11- and 24-week follow-up spectra maintained the posterior-anterior gradient, but the amplitudes of the overall spectra diverged somewhat, a limitation for the 24-week data is that it was acquired with only 13 subjects.

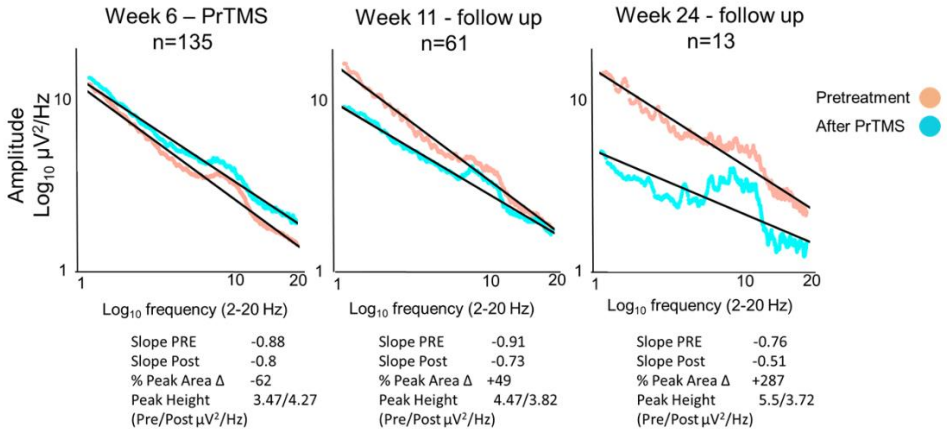

Figure 5c Frontal 1/f^{a} Regressions of EEG spectra. The 3 panels show mean log-log plots of frontal EEG power spectra for subjects before PrTMS, at 6 weeks of PrTMS, and at the 11-week and 24-week (n=13) follow-ups. The solid lines in each panel indicate the 1/f^{a} robust regressions. The alpha peak center frequency signal amplitude is shown in $\mu V^{2}/Hz$. The 1/f^{a} slope consistently exhibited a positive change in slope, i.e., shallower, at 6, 11 24 weeks, all of which were statistically significant using a paired t-test ($p<0.05$).

The $1/f^a$ regressions of averaged power spectra (**Figure 5c**) for the frontal cortical EEG leads are shown for before and after treatment. The regression lines have shallower slopes at 6 weeks of PrTMS and at the 11 week follow up ($p<0.0001$), and show reduced steepness relative to pretreatment at the 24 week follow-up ($p<0.0001$). This suggests that the degree of arousal of the brain and its neurotransmitter profile may have changed [19, 22, 23]. To our knowledge this is the first report of spectral analysis applied to patients with concussion, and our results suggest the possibility that the EEG spectrum may potentially serve as a concussion biomarker and a means to track post-injury trajectory and recovery [27].

4. Discussion

Mild to moderate concussion is widespread, it is difficult to manage, and there are no US Food and Drug Administration (FDA)-approved specific medications for any neuropsychiatric or neurocognitive concussion symptoms [28]. The present report describes the use of a modified form of rTMS called PrTMS, with patients suffering from persistent concussion symptoms and who sought an effective treatment option. Two different concussion indices both indicated an improvement of symptoms with PrTMS. After 6 weeks of PrTMS there was a frontal cortical increase in the spectral EEG alpha peak amplitude, and an initial increase in the alpha peak center frequency. Central, parietal, and occipital cortical regions showed a decline in center frequency and a rise in alpha peak amplitude.

The underlying mechanisms of concussion involve changes in neurotransmitter activity and this points to the potential relevance of $1/f^a$ regression analysis of the spectral EEG [29]. In keeping with reported neurotransmitter roles in concussion, we observed that 6 weeks of PrTMS induced a slight but statistically significant slope decrease, i.e., shallower slope, of the $1/f^a$ regression of the frontal cortical spectral EEG, reported for the first time in concussion. This shallower spectral slope may reflect subtle changes in frontal cortical neurotransmitter balance, neural irregularity, and cognitive status and perceptual encoding [22, 30]. Washke et al (2017) and others note that encoding and representing sensory information is more thorough during an irregular or desynchronized state as opposed to a regular, or synchronized condition [30-32]. Not only is this of considerable interest as a potential biomarker in concussion, but may also point to potential explorations of mechanisms and possible pharmacological strategies, conceivably in the context of a combined pharmacotherapy - PrTMS approach.

Several neurotransmitter types and pathways may play key roles in the deficits associated with concussion, and may represent potential therapeutic targets. For example Arakaki et al (2018) suggested that cholinergic mechanisms may participate in the learning impairment seen after mTBI [33]. Along these lines others similarly suggest that dysregulation of consciousness induced by concussion could be due to enhanced acetylcholine as well as concomitant lowered norepinephrine in the cerebral cortex [34]. Disturbances in memory, focus, and problem solving are common after mild to moderate TBI which could reflect cholinergic dysfunction. Midline concussive injury in rats induced a bilateral loss of cholinergic neurons averaging 36% in area Ch1 (medial septal nucleus), 45% in Ch2 (nucleus of the diagonal band of Broca), and 41% in Ch4 (nucleus basalis of Meynart. In addition, lateralized injury induced cholinergic neuron loss of similar magnitude ipsilaterally but a lower contralateral loss of between 11% and 28% [35].

Reduced levels of the neurotransmitter GABA over one year following traumatic brain injury were measured by Kang et al (2022) [36]. In the same study longitudinal improvement in executive attention correlated with increased GABA receptor availability [36]. Concussion may affect GABAergic thalamic neurons, and notably, rTMS has been reported to modulate GABA levels [37, 38], along with endogenous dopamine and other neurotransmitters [39]. For example, Etievant et al (2015) found that 5 days of rTMS increased dopamine D2 receptors in the frontal cortex of mouse brain [40]. In fact, a plethora of evidence has suggested that dysregulation in dopamine neurotransmission follow-

ing mild to moderate traumatic brain injury is involved in the development of post traumatic memory deficits. Tang et al (1997) found when they administered sulpiride, a D2 antagonist, and SCH-23390, a D1 antagonist, to mice subjected to experimental mTBI, that sulpiride but not SCH-23390 significantly improved the deficits in task performance, indicating that D2 receptors are the major site of action [41]. But when both compounds were combined there was a significant additive effect. Tang and colleagues pointed out that that a dopaminergic mechanism contributes to the memory dysfunction associated with traumatic brain injury [41].

Behavioral deficits after traumatic brain injury (TBI) are thought to be closely linked to dysregulation of dopamine pathways [42]. Edut et al. (2014) reported that mice administered low MDMA doses prior to mTBI exhibited better performance in cognitive tests [42]. In this study administration of MDMA prior to experimental mTBI normalized changes in tyrosine hydroxylase (TH) levels, and attenuated elevated dopamine receptor type 2 (D2) levels observed after mTBI [42]. The authors suggested that these effects operating at the cell signaling level could point to potential therapeutic candidates. While it seems counter intuitive that increased dopaminergic activity induces cognitive decline, Cools et al., (2019) reported that the role of dopamine in cognition is "paradoxical" in that reduced cognition can occur when there is a high baseline dopamine level [43]. Pang et al., (2003) reported that dopamine and encephalin can participate in the pathophysiological course of cerebral injury after cerebral concussion, and as such play an important role in the blood vessel injury, regulation of blood-brain barrier and the denaturation and necrosis of nerve cells [44].

The levels of biogenic amines and their metabolites after experimental concussion in rats were analyzed by Kmieciak-Kolada and colleagues (1987) in different parts of the brain and cerebral-spinal fluid [45]. After 6 hours striatal 5-hydroxytryptamine was increased while dopamine utilization was reduced [45]. Imbalance between the functional state of serotoninergic and dopaminergic neurons may partly explain the development of vasospasms, ischemia and edema brought about by the brain mechanical trauma. Kmieciak-Kolada and colleagues (1987) found reduced norepinephrine concentration in discrete brain areas and a diminished dopamine release in the whole brain [45]. The authors concluded that altered catecholamine and 5-HT utilization in discrete brain areas, especially in the striatum are characteristic of impairment after experimental concussion. They also noted that the pathology of TBI adversely influences many brain regions, often causing comorbid psychiatric disorders including substance use disorders (SUD) [46-50].

In terms of catecholamines and serotonin, Majchrzak et al (1979) reported that in patients with signs of intracranial hypertension following craniocerebral trauma, there were significantly elevated concentrations of HVA and 5-HIAA in the cerebrospinal fluid compared to a control group [51]. After craniocerebral injuries with open fracture of cranial bones without disturbances of consciousness, dopaminergic system hyperactivity was observed lasting up to the 7th day after injury.

This pilot study has several limitations, most notably the absence of a sham controlled study cohort along with the heterogeneous nature of the treated population. We believe that the current findings in a moderately sized cohort (185 patients) suggest a beneficial clinical outcome as depicted in our results section. However, given the marked placebo effects of rTMS, we strongly encourage large prospective studies, e.g., double blind -sham controlled as well as cross-over, in the future. Standard rTMS should be compared with PrTMS, and importantly, in our opinion current sham rTMS devices insufficient and there is a significant need to enhance sham technology.

5. Conclusions

The present report summarizes pilot clinical data acquired with PrTMS treatment of patients suffering from persistent symptoms of concussion. Patients reported substantial and significant improvement in self-reported concussion and sleep indices after PrTMS.

Moreover, the spectral EEG, a comparatively agnostic measure of cortical status, changed in terms of alpha peak properties, apparent synchrony between cortical territories, and $1/f^a$ regression slope. In aggregate, these findings support the pursuit of further, prospective controlled studies of PrTMS for concussion treatment, along with exploration of the spectral EEG as a biomarker of concussion.

Author Contributions: MTM analyzed the data and wrote the manuscript, CN extracted the questionnaire and EEG data and assisted with data analysis, JK acquired a major portion of the data, KB participated in data analysis and writing the manuscript, CAD performed directly pertinent and cited literature searches and analyses, DB, PKT, and KS critically reviewed and edited the manuscript, IE reviewed and rewrote the manuscript, MRM performed statistical analyses and prepared figures, and LKTM conceived the study, oversaw patient treatment and data collection, and edited the manuscript.

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Conflicts of Interest Statement: Dr. Murphy owns shares in PeakLogic Inc., Dr. Makale receives salary compensation from PeakLogic, Mr. Nybo is a founder/owner CrossTx, Dr. Keifer is the owner/operator of BrainHealth Hawaii Incorporated. Dr. Blum is Executive Chairman of TranspliceGen Therapeutics Inc., a company that has been licensed to develop his entire patent portfolio including genetic testing and pro-dopamine regulation.

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