QEEG Resources

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Thank you Greg for the introduction,

Hello Katherine,

Thank you for your interest in our Dry Sensor Interface (DSI) technology.

I would be happy to share more with you about our systems and how you could use them for QEEG analysis. Below is some product information, however, I would be happy set a time to discuss these and your needs in more detail, to ensure that there is a good match and that our products can successfully support your research needs.

DSI technology is opening new possibilities for EEG applications, as DSI signal quality is comparable to that obtained with conventional wet-electrode systems but without the need for skin abrasion or preparation and no gels. Our headsets are very easy to wear and remove, even allowing users to put it on themselves in under 5 minutes typically, and furthermore users invariably report that our headsets are very comfortable and praise the lack of gels. Finally, wireless transmission and on-board memory storage allow recordings without being tethered to a computer, and users are thus able to move freely around the room.

The DSI-24 is the next generation DSI EEG system with the signal quality expected from a wet/gel based EEG system but without the gel, making it uniquely easy to use and acceptable to users. In addition, the DSI headset positions 19 active dry sensors at the International 10/20 locations (plus 2 ear clip sensors), while providing a comfortable fit to a wide range of head sizes. Its integrated 24 channel amplifiers and digitizers allow acquisition of the EEG signals as well as 3 auxiliary sensors (ECG, EMG, EOG) right on the headset, and its Bluetooth transmitter or on-board memory allows for wireless recording. Furthermore, the DSI-24 is resistant to electrical and motion artifacts making it ideal for use in ambulatory environments.

The DSI-7 is a small light weight DSI system with 7 active dry sensor locations on the scalp (plus linked ear). This system is optimized for rapid donning and with its integrated amplifiers, digitizers, and Bluetooth transmission, offers a cost effective solution for rapid EEG acquisition. Of course, it too is comfortable for long-term wear. If you prefer a system that has more flexible sensor positioning, with the trade-off of slightly increased set-up time, we offer a DSI-7-Flex, which is similar in sensors and price to the DSI-7 only without the rigid arms that position the sensors and the headphone structure that holds the headset on the head.

The table below highlights the main features of the systems.

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service

- better outcome data

1 day training

3 adjustment points

14 years of age

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1/3
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*Conduct research in Neuroscience, Brain-Computer Interfaces (BCI), Neurofeedback, NeuroEconomics, Neuromarketing, Rehabilitation, Sport Psychology and other fields.
*Monitor mental workload, fatigue, engagement, and other states in real time.
*Optimize training and track skill development in expert and novice performers.

Please note that the systems are not yet FDA approved, and are thus sold for non-clinical applications. Systems include data acquisition software that features a TCP/IP socket to stream data externally, as well as C-based Application Programming Interface (API) to interface with other applications (3rd party or your custom-built application). Raw (unfiltered) or filtered data can be easily exported to a comma separated value (CSV) or EDF file formats allowing easy import into most data analysis programs.

To introduce our dry sensor EEG technology to the Neurofeedback and QEEG communities, Wearable Sensing has partnered with both Applied Neuroscience Inc. and BrainMaster Technologies, Inc., and integrated our DSI-24 and DSI-7 EEG systems into both the Neuroguide and Avatar software suites.

Please let me know if you have questions about our technology or systems or would like to request a formal quote, or set a time to talk by phone to explore how our technology could support your research.

Thank you,

Walid

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qEEG Summary

Quantitative electroencephalography, qEEG, is a way of measuring activity in the brain, also called “brain mapping”. qEEG can be used as a tool to measure any changes in the brain activity seen in patients. The articles provided show how qEEG was used in several different applications.

**Article 1: TMS therapy and pre-and post-qEEG in recurrent major depression disorder**

Method: 32 patients with recurrent depression had a qEEG reading taken before and after rTMS treatment.

Results: Through the qEEG reading, a general increase in delta and theta power was observed which was seen after completing 20 rTMS treatments.

**Article 2: A case study comparing ketamine to deep TMS- direct observation of immediate effect vs. durable recovery using qEEG**

Method: qEEG was used as a biomarker both pre and post ketamine as well as pre and post TMS treatment.

Results: Both post Ketamine and TMS show a change in the frontal area. In pre Ketamine qEEG reading, overactivity was seen in the frontal region of the brain (showing high anxiety) and in the post Ketamine qEEG reading, the overactivity was normalized. Pre and post TMS showed a similar reading.

**Article 3: Prefrontal EEG Asymmetry as a Potential Biomarker of Antidepressant Treatment Response with Transcranial Magnetic Stimulation (TMS): a Case Series**

Method: qEEG readings were recorded for phase 1 which includes tapering off of medications to start TMS treatments, as well as phase 2, which consists of undergoing TMS treatment for 3 weeks. qEEG was recorded 3 minutes before TMS, during TMS and 3 minutes after TMS. Only 2 electrode sites (F1 and F3) were recorded and they were linked to the ears.

Results: qEEG recordings show that in the left hemisphere, there is less brain activity than the right in patients diagnosed with MDD. qEEG frequencies were found to be stronger in the left hemisphere when a reading was taken after TMS treatment. The authors discuss that using only 2 leads on the ears was sufficient in applying qEEG readings to real life clinical setting.
Modulation of transcranial magnetic stimulation evoked potentials by 30 Hz theta burst stimulation of the cerebellum
Graeme D. Hammond-Tooke, Alanah Harrington
University of Otago, Dunedin, New Zealand

Transcranial magnetic stimulation (TMS) has the potential to modify cortical excitability as a therapy for neurological and psychiatric disease. Limitations include the transient and localised nature of the effects. In some situations, where cortical excitability is diffusely abnormal, more widespread modulation of cortical activity is desirable. The cerebellum has extensive connections to cortical areas, via the dentato-thalamo-cortical pathway, and the cerebellum is therefore a promising stimulation site for treating conditions with altered cortical excitability. Previous studies have shown that 50 Hz intermittent theta burst stimulation (iTBS) of the cerebellum increases the amplitude of motor evoked potentials (MEP) obtained from ipsilateral muscles by stimulation of the contralateral motor cortex, while continuous TBS (cTBS) has the opposite effect. In this combined TMS-electroencephalography study, the effects of 30 Hz right cerebellar hemisphere TBS on TMS-evoked potentials (TEP) were investigated; in particular the effects on the N100 component, which is thought to reflect intra-cortical inhibition. 16 participants, aged 18-30 years, received 30 Hz iTBS, cTBS or sham TBS with a placebo coil in three separate sessions. MEP and TEP were recorded before and after treatment. Treatment with iTBS resulted in an increase in the amplitude of the N100 compared to sham, without significantly altering MEP amplitudes. cTBS did not significantly affect N100 amplitude and had varying effects on MEP, depending on stimulus intensity. The N100 changes were present diffusely and bilaterally. The findings suggest that 30 Hz cerebellar iTBS enhances activity in both inhibitory and facilitatory cortical networks. These effects may be useful therapeutically, but the stimulation intensity may be critical in determining the net effect on cortical excitability.

The impact of theta burst stimulation over supplementary motor cortex on gait perturbations of Parkinson's diseases patients with and without freezing of gait
Po-Yu Fang,a Ying-Zu Huang,b Jh-Kai Yu,c Ya-Ru Chang,c Rou-Shyan Chenb
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b Department of Neurology, Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Taoyuan, Taiwan
c Department of Physical Therapy and Graduate Institute of Rehabilitation Science, College of Medicine, Chang Gung University, Taoyuan, Taiwan

Introduction: Gait and balance disorders represent a major therapeutic challenge in Parkinson's disease (PD). Among them, the problem of freezing of gait (FOG) is an important issue in devastating patients' quality of life, as well as escalating the patients' dependence. Although the pathophysiology of gait and balance disorders in PD remains insufficiently understood, several recent studies suggested that anticipatory postural adjustment (APA) may play an important role. In this perspective, supplementary motor cortex (SMA) and premotor cortex (PM) might have influence on gait preparation and execution. We therefore conduct this study for elucidating the possible effect of theta burst stimulation (TBS) SMA in gait performance.

Method: We recruited Parkinson's disease patients with and without freezing of gait into this study. We performed the quantitative gait analysis for the body sway during quiet stance, dynamic postural control of gait speed and gait variability, and APA. We then performed 1Hz continuous theta burst stimulation (cTBS600) over the SMA and immediately re-check the same quantitative gait analysis within 10 min.

Result: The preliminary data indicate possible promising result in improving the timing of APA in arm outstretched, step initiation and body turning before and after cTBS600 on SMA. However, the dynamic gait performance as step length, cadence, and walking time did not show significant difference, as well as the numbers of FOG.

Discussion: Although recent limited studies suggested that 1Hz repetitive transcranial magnetic stimulation (rTMS) over SMA could improve UPDRS part III score of Parkinson's disease, but did not paid special attention to the gait parameters. Our data could share some light on pathophysiology of gait disorders in PD. We suggest that further study with large patient sample should be warrant for the promising therapeutic implication by cTBS600 on SMA.

TMS therapy and pre-and post-QEEG in recurrent major depression disorder
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b Sobhe Sadegh Center
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Background & Objectives: The Transcranial Magnetic Stimulation is a safe and non-invasive method for treatment of major depression from two decade and is approved by FDA from 2008. In depressed patients there are specific changes in quantitative electroencephalography (QEEG) in comparison with normal persons in some areas of brain.

The purpose of this study was to investigate the effectiveness of rTMS (repetitive transcranial magnetic stimulation) in reduction the signs and symptoms of depression and the changes in brain's wave (QEEG).

Method: It was used a quasi experimental, pretest - posttest design with control group, a sample consisting of 32 patients who had recurrent depression on the basis of SCID, BDI & Hamilton scales. They were randomly assigned to two groups.

The experimental group underwent 20 sessions of rTMS on the left DLPFC as the independent factor and both groups (control & experimental) had 12 session psychotherapy and drugs treatment. During treatment it was used BDI once in a week to determine the effect of rTMS. Before and after rTMS treatment, the patients were given HAM and QEEG were taken.

Result: This research showed adding rTMS to the usual treatment have reduced significantly the rate of depression. (Z = 0.05) (Beck scale P ≤ 0.001 & T = 4/11) (Hamilton Scale P ≤ 0.001 & F = 28/77). In QEEG, a general increase in delta and theta power was observed. An effect that is seen following rTMS administration.

Conclusion: The rTMS decreased the signs and symptoms of depression and increase delta waves in QEEG.

Brain-state dependent brain stimulation: Real-time EEG alpha band analysis using sliding window FFT phase progression extrapolation to trigger an alpha phase locked TMS pulse with 1 millisecond accuracy
Christoph Ziemer, Johannes Tünnerhoff, Carl Zipser, Florian Müller-Dahlhaus, Ulf Ziemann
Center for Neurology, Tübingen University, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany

Simultaneous EEG-TMS is a powerful method to non-invasively couple with brain dynamics. We present an experimental set-up that extends current approaches by "closing the loop" between the EEG signal and the parameters of the brain stimulation being simultaneously applied. The online detection of EEG alpha band
Conclusions: The evidence for the effectiveness of antidepressants in this population remains sparse. The literature does not support a single antidepressant as more efficacious. A combination of antidepressants with CBT seems to be superior to either alone. Finally, non-pharmacological treatments might provide additional benefit, without the potential harms and can represent valuable alternatives to antidepressant drug therapy.

Comparison of beam technique and 5.5 centimeter rule for determining site of TMS stimulation for major depressive disorder
J. Halper a, C. Yagi b, A. Manevitz c, K. Nishimoto b, A. Onishi a
a LENOX Hill Hospital
b TMS Medical Associates of New York, Sutton Place TMS
b New York-Weil Medical Center

Objective: To compare TMS stimulation sites identified by the beam method, which localizes F3 (beam) and the 5.5 cm rule and the implication of any differences for their comparative efficacies as stimulation sites.

The beam and 5.5 cm techniques are commonly used in clinical settings. MRI-neuronavigation is potentially the gold standard. In view of the large area of the dlpfc the optimal site of stimulation within it must be determined. One such site has been identified by fox. Recently, Mir-Moghtadaei found that the site identified by beam was quite close to that site.

Methods: We measured the stimulation positions determined by both the beam and 5.5 cm rule for 36 subjects.

Results: The beam technique identified an SOA location 1.7 (sd 2.9) cm superior to and an AP location 1.6 cm (sd 1.7) anterior to those obtained using the 5.5 cm rule (non-significant difference) in only 8 patients where the two sites were within 3 cm, i.e. essentially overlapping with respect to TMS.

Conclusions: In our study, the site identified by the two techniques differed for most subjects. Combined with Mir-Moghtadaei's finding that the beam and neuronavigated sites were virtually identical leads to the preliminary conclusion that the beam technique is better for determining the appropriate site of TMS stimulation than the 5.5 cm rule if the site used by Mir-Moghtadei is indeed optimal for depression. It is also preliminary because no one study has compared the stimulation sites identified by the 3 techniques directly with regard to location or treatment efficacy.

A case study comparing ketamine to deep TMS – direct observation of immediate effect vs. durable recovery using QEEG
Shelly Menolascinao, Mitch Belgrina, Lillian Fishera, Elizabeth Ranuma
Washington Square Psychiatry & TMS, New York, NY

Background: A patient with lifelong treatment-resistant mood disorder and social anxiety was treated successfully with intranasal ketamine for several months until side effects became intolerable. During a recurrence of depression, treatment with dTMS led to full and durable recovery. We used QEEG to directly observe changes in brain activity, finding that the two treatment modalities both normalized excess corticocircum activity.

Methods: We used QEEG as a state biomarker to observe the immediate effect of ketamine, before and after administration intranasally. Months later, during acute recurrence of depression (MADRS = 46), we treated with dTMS (18 Hz, daily) recording QEEG before TMS and again in remission.

Results: The pre-Ketamine QEEG (state of social anxiety) showed corticocircum overactivity at 14–15 Hz throughout the frontal region of the brain. Ten minutes post-ketamine, QEEG showed that overactivity was normalized. Months later, in a recurrence of depression, his QEEG (state of acute depression) revealed a very similar pattern of corticocircum overactivity. The post-TMS QEEG (state of full remission) showed near-normalization of this corticocircum circuitry. The patient noted: "TMS really shut down the internal dialogue feedback loop much the same way ketamine did."

Conclusion: Post-TMS QEEG appears remarkably similar to post-ketamine QEEG with normalization of beta activity in frontal area. This suggests that the two treatments both exert antidepressant effects by normalizing excess activity in the corticocircum circuitry.

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Prefrontal EEG Asymmetry as a Potential Biomarker of Antidepressant Treatment Response With Transcranial Magnetic Stimulation (TMS): a Case Series

Agnes P. Funk, Mark S. George

Key Words
Biomarker
Depression
Electroencephalography
Transcranial Magnetic Stimulation
Treatment Response

ABSTRACT
We review studies that have used EEG as a response biomarker in depression, and then present preliminary EEG change data from an ongoing TMS depression treatment trial. These data in 4 depressed subjects over 3 weeks of treatment suggest but do not prove that there may be asymmetry changes that occur both within a daily TMS session and over the course of several weeks that may be associated with antidepressant response. EEG shows potential as a biomarker of response for depression treatments, particularly the brain stimulation devices, which, unlike medications, can locally interact with neural tissue in specific frequency patterns.

INTRODUCTION
The major depressive disorders (MDD) are costly to patients, their families and society in general. In addition to establishing the causes of MDD, the scientific and medical community is also searching for diagnostic biomarkers or response predictors of the depressive disorders. Researchers are exploring a variety of techniques and methodologies as potential biomarkers, particularly neuroimaging or genetics. (See Chapter 18 in for a recent review). This review focuses on electroencephalography (EEG) as a biomarker, particularly when it is combined with transcranial magnetic stimulation (TMS). Before discussing the combination, we briefly summarize the history of EEG in depression, and review studies using TMS as an antidepressant. We also discuss an underlying theory that might serve to guide this combinational research of TMS and EEG in depression, namely the laters approached withdrawal model of emotion. Leuchter and colleagues have revealed a novel quantitative EEG method of cordance, which may predict responders to antidepressants. Following this line of work, we wondered whether depressed patients who respond to TMS treatment might also show predictive EEG changes and present a case series where we have gathered prefrontal EEG in depressed patients undergoing treatment with daily left prefrontal rTMS.

Electroencephalography (EEG) and laterality of emotion
Some 20 years ago Davidson built on earlier work by Sackheim and colleagues and popularized the approach-withdrawal hemispheric laters model of emotion. This model posits that different emotions are regulated by specific patterns of neurophysiologic activity and that a hemispheric asymmetry exists between approach and withdrawal-related emotions and their associated moods. Davidson used EEG to show a difference in the level of alpha (8-13 Hz) activation between the hemispheres dependent upon the type of emotion elicited by positively or negatively valenced stimuli. Thus, greater activity in the left frontotemporal areas occurred with positively valenced stimuli, which then gives rise to approach-related emotions, while homologous right cortical areas were activated by negatively valenced stimuli resulting in withdrawal-related emotions. The type of emotional response elicited in an individual would then influence their resultant behavior. For example, a withdrawal-related emotion such as fear, with right-sided increases in activity, may result in the individual attempting to flee the situation.

This model sets the stage for potential developing prefrontal EEG as a biomarker in depression. Davidson and colleagues argue that the hemispheric asymmetry shown in alpha EEG activity is exaggerated in patients with depression. Thus, depressed patients show lower activity in the left hemisphere (i.e., the positive, approach-related emotional side) compared with right-sided activation. In support of this, several neuromaging studies have found left dorsolateral prefrontal cortex (DLPFC) hypoactivity in MDD patients, although just as many studies have not found this left hypoactive pattern and it is far from universal.

Predicting pharmacological treatment response using EEG
With this prefrontal hemispheric valence model as background, would it be possible to use EEG to predict which antidepressant might be the most effective for a specific depressed patient or to monitor treatment responses over time or even adjust dose? This is a crucial question as it is estimated that up to 50% of depressed patients do not respond to their first prescribed antidepressant. Depressed patients typically do not show robust clinical responses until at least 2-3 weeks after starting medications, putting patients at continued risk of suicide during these early weeks of treatment. Clearly it is imperative that patients receive the most efficacious antidepressant as promptly as possible. Leuchter and colleagues have developed a quantitative EEG (QEEG) measure called “cordance” to address this need of early identification of responders to antidepressants. The cordance value is composed of the normalized absolute and relative EEG power as determined at each electrode site. Each electrode site can be measured against its cordance value to determine whether it is concordant (i.e., there is a positive association between the absolute and relative powers) or discordant (absolute and relative powers are negatively associated). Cordance can also yield a global measure based on the proportion of electrodes showing discordance. For example, if an individual had less than 30% of their electrodes being discordant then they would be considered to exhibit the concordant state which is equivalent to a normally functioning brain. Discordant proportions higher than...
30% would indicate a discordant global state and are associated with lesions, low perfusion and low metabolism.

This group initially showed that global measures of concordance could predict response to the antidepressant medication fluoxetine.2,14 Twenty-four unipolar depressed patients were studied over 8 weeks while receiving 20 mg of fluoxetine; they were then divided into concordant and discordant groups. The concordant group had lower Hamilton Depression (HAM-D) and Beck Depression Inventory (BDI) scores. Decreases in prefrontal theta band concordance have been observed in responders to antidepressants as early as 48 hours following treatment with either fluoxetine or venlafaxine. These early decreases in prefrontal concordance were also found during the placebo-lead in period (a 3-14 day period allowing the washout of any preexisting medication) in subjects who responded to drug treatment. This group has also found that decreases in prefrontal concordance predicted responders to pharmacotherapy even without a wash-out period between treatments, thus making the concordance measure a potentially effective biomarker in “real world” clinical settings of pharmacotherapy. More definitive studies with this EEG biomarker are underway with positive results to date. One EEG manufacturer, Aspect, is pursuing FDA approval for this use.

Transcranial magnetic stimulation (TMS) and depression

Barker and colleagues in 1985 and 1986 developed the modern form of transcranial magnetic stimulation (TMS).22,23 The TMS device is made up of a capacitor which delivers a pulse current via an insulated coil to produce a pulse (or time-varying) magnetic field. This magnetic field passes through the scalp and causes neurons to depolarize. The pulses can be delivered at a single pulse (<1 Hz) or rapidly (1-25 Hz). Commonly the pulse intensity is measured relative to the maximum output of the capacitor and is referred to as the motor threshold (MT). The MT is measured by recording motor evoked potentials from either the abductor pollicis brevis or first dorsal interosseous muscle. The minimum intensity required to evoke a 50 μV motor potential 50% of the time (i.e., 5 out of 10 trials) is considered the MT. The MT can be measured from either a relaxed (resting MT) or contracted (active MT) muscle, however, it is always expressed as a percentage of the maximum stimulator output.

Typically, single-pulse TMS is used to measure and map sensory and higher-order functions while rapid rate or repetitive TMS (rTMS) has been investigated as a therapeutic treatment for psychiatric disorders. Overall, the vast majority of published studies in healthy adults have used single-pulse TMS. In fact, initially TMS was used to measure motor conduction time but researchers quickly discovered its ability to induce “virtual lesions” in superficial cortex.26-29 TMS as a research tool has helped provide insight regarding the underlying neurophysiology of motor, visual and higher-order functions, such as attention. More recently TMS coupled with brain imaging techniques has revealed that cortical activation is not restricted to the site of stimulation, but is instead propagated along corticocortical and subcortical connections.30,31

George and colleagues first demonstrated the potential antidepressant effects of daily left prefrontal rTMS over several weeks for major depressive disorder (MDD).32-34 Although research has continued to show that rTMS is an effective treatment for MDD, there is no clear consensus on the most efficacious rTMS parameters to use, namely pulse frequency and intensity, and the frequency and duration of the treatment itself. For example, typical therapeutic application of rTMS is administered twice per day for 2 or more weeks at a pulse frequency of 10 Hz and intensity of 110% of motor threshold. Notably, the number of pulses per treatment has been steadily increasing over the years, and a meta-analysis by Gross and colleagues (2007) revealed that recent rTMS trials have shown stronger anti-depressant effects compared with earlier studies.27 The optimal site to deliver rTMS for the treatment of MDD has consistently been the (DLPFC) and typically left-sided high frequency rTMS (>10 Hz) has shown the greatest “anti-depressant” effects, and to a lesser extent right-sided slow rTMS.

Neuroimaging studies have revealed that rTMS over the DLPFC increases activity at the site of stimulation and in connected limbic areas, including the bilateral middle prefrontal cortex, right orbital frontal cortex, left hippocampus, medial dorsal nucleus of the thalamus, bilateral putamen, pulvinar and insula, ipsilateral subgenual cingulate and basal ganglia.35 There is also evidence of metabolic and neurotransmitter modulation, including 5-HT and dopaminergic release,41,42 increases in DLPFC glutamate concentration,43 reduction in the catecholamine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) and increase in brain-derived neurotrophic factor.44-46

Combined TMS and EEG studies

Although rTMS combined with neuroimaging techniques has revealed much about the cortical connectivity of the DLPFC, the information it yields is limited temporally to several seconds. This is vastly slower than the cortical processing speed, which is in the vicinity of milliseconds. A way to overcome this problem is with the simultaneous combination of TMS and EEG, both of which have excellent temporal resolution. There have been numerous studies, which have examined single-pulse TMS combined with EEG (for review see 47), however, combination studies investigating the effects of a dose or train of rTMS on EEG activity are limited. A recent study by Griskova and colleagues (2007)48 looked at the effect of 10 Hz rTMS on the EEG power spectrum. They applied 10 Hz rTMS (2000 pulses, 10 s intertrain interval) at 101% of resting MT over the left prefrontal cortex, and recorded 10 minutes of resting EEG before and after rTMS. Subjects also received sham rTMS as a control measure. There was an overall increase in delta power compared with the sham condition, which was greater in the central region (comprised of electrode sites Cz, C3, and C4) and fronto-central region (Fz, F3, F4). Okamura and colleagues (2001)49 examined 6 different time periods using EEG combined with 2 trains of 10 Hz rTMS (each train being 3 s long) at 100% of MT over left frontal cortex: (1) pre-rTMS, (2) within 1 minute post-rTMS, (3) 1-2 minutes post-rTMS, (4) 2-3 minutes post-rTMS, (5) 3-4 minutes post-rTMS, and (6) 4-5 minutes post-rTMS. They found that rTMS increased the peak frequency and maximal and relative powers, but that these increases did not occur at the same time. Thus, the peak frequency immediately increased (within 1 minute) following rTMS, then returned to baseline within 2-5 minutes. However, changes in absolute power occurred more slowly, with an initial decrease at 3-4 minutes followed by an increase at 4-5 minutes. Graf and colleagues (2001)50 delivered 20 Hz rTMS (1600 pulses; 28 s intertrain interval) at 90% of MT over the left dorsolateral prefrontal cortex.47 They recorded 10 minutes of EEG, 30 minutes before rTMS and 30 minutes following rTMS. However, they found no significant changes in the EEG power spectrum.

The results of these combined rTMS and EEG studies are mixed, however, the studies have widely divergent methodologies and examined different hypotheses. The lack of change in EEG power as described by Graf and colleagues may be explained by the results of Okamura et al.,50 who found changes in EEG peak frequency and power within 5 minutes of delivering rTMS. Note also that Griskova and colleagues recorded EEG immediately after delivering rTMS and found changes in delta power. Graf et al.50 waited 30 minutes after...
Figure 1.
These two graphs display data from 4 subjects in the open-label extension phase of the ongoing OPT-TMS depression treatment trial. The x-axis represents each TMS treatment session, typically given each weekday for 3 weeks (15 treatments). Prefrontal EEG is acquired before (black diamonds) and then after (open squares) each session. For each frequency, we have expressed the data as a ratio of left hemisphere to right hemisphere. Data are shown for the delta (top graph) and Beta 1 frequencies (bottom graph). Note that initially, there is a right hemisphere bias which reverts after a single treatment and which is absent at later treatment sessions. The full analysis of the study will test whether these descriptive changes seen in 4 subjects are a potential biomarker of response.

delivering rTMS before they began recording EEG, thus this duration may have been too long to observe any significant effects of rTMS on EEG. The difference in the results of Okamura and Griskova may be explained by the different rTMS parameters they used, 2000 pulses at 110% of MT (Griskova) compared with 60 pulses at 100% of MT (Okamura). Given that cortical activity is highly influenced by rTMS stimulus parameters, it is difficult to compare the outcomes of these studies. Nonetheless, these studies show that a dose of rTMS similar to that being used in antidepressant clinical trials does have an effect on EEG activity, but stimulus parameters and time constraints likely matter. Clearly, the area of combined rTMS with EEG requires much more extensive investigation.

Preliminary data using EEG to follow rTMS treatment response
We are currently conducting a 4 site (Medical University of South Carolina (MUSC), Emory University, University of Washington, Columbia University) NIH-funded study which combines rTMS and EEG and addresses the question of whether we can use changes in EEG power or asymmetry to predict which patients with MDD will respond or remit following treatment with rTMS. A total of 240 patients with MDD are being treated in a 3 phase rTMS treatment protocol following medical and neuropsychological screening. In phase 1, patients are tapered off their medication and randomized to receive either real 10 Hz rTMS at 120% of MT over the left DLPFC (3000 pulses, 26 s intertrain interval) or sham rTMS. The sham setup is the first of its kind and both patients and TMS operators are blind to treatment status. This active sham coil uses low level electrical stimulation (5 amps) delivered over the left DLPFC under the TMS coil for those randomized to sham. Thus, patients feel the coil and scalp muscle activation as it would be for real rTMS, but are not receiving stimulation powerful enough to activate underlying cortical structures. If patients remit, they move directly into phase 3 where rTMS treatment will be tapered off over 3 weeks and the patients are placed on a standardized antidepressant regime. If patients do not remit, they are
offered entry into phase 2 where they will knowingly receive real rTMS for 3 weeks. If patients still do not respond to rTMS treatment, they can opt to receive additional left-sided rTMS or start right-sided treatment.

The EEG data has been collected for phase 1 and 2. Due to time and equipment limitations only 2 electrode sites (F1 and F3) can be recorded using the linked ears reference. Before rTMS delivery, patients are seated comfortably in a reclined position with eyes fixated on the ceiling and eye blinks kept to a minimum. They are instructed to keep all movement to an absolute minimum. Five minutes of EEG are recorded before and after rTMS treatment. Patients are then required to fixate their eyes and keep still for 10 seconds immediately following the first 10 pulses and then again for the last 10 trains (EEG is continuously recorded throughout the session for a total of 75 pulse trains). Amplification of the EEG signal was by the James Long Sham TMS system (James Long Company, Caroga Lake, NY) with a bandpass filter of 1.4 - 44 Hz. The sampling rate was 1540 Hz and it was digitally filtered with a sharp cutoff 70 Hz lowpass filter. It was then digitally resampled at 140 Hz. Artifact identification and rejection initially occurred automatically and was then followed by visual inspection. The selected power frequencies were then extracted from the EEG signal using an EEG analysis system (James Long Company, Caroga Lake, NY).

As the study is not yet complete, the blind cannot be broken for the double-blind phase 1, however, phase 2 EEG data can be examined, when patients are openly receiving rTMS. As EEG data collection for phase 2 began much later in the study, only a small number of patient data (4 patients) are currently available. With such a small number of patients, formal data analysis has not been performed. However, some interesting data trends are apparent and these will be formally investigated in the final complete dataset. Using the James Long software, power frequencies were extracted from the data, i.e., delta, theta, alpha, beta 1 and beta 2. A hemispheric ratio (left hemisphere power/right hemisphere power) was calculated for each power frequency before (pre-rTMS) and after (post-rTMS) treatment for every treatment session. There was a total of 15 sessions per patient x 4 patients = 60 sessions. Data from 10 sessions were corrupted or missing, thus only 50 sessions were analyzed and presented. For all frequencies, at the initial stages of treatment, the pre-rTMS ratio was lower than the post-rTMS ratio, indicating that baseline EEG power was stronger in the right hemisphere compared with the left hemisphere. This corresponds with data showing that people with MDD tend to have less activity in the left hemisphere compared with the right. However, once patients receive a single session of left prefrontal rTMS (3000 stimuli) the EEG power frequencies become stronger in the left hemisphere, as shown by the post-rTMS ratio, demonstrating that rTMS has actually changed the level of EEG activity between hemispheres within a single session. This trend continues throughout the patient's treatment, until there is a complete reversal of pre- and post-values, such that at the end of the course (treatment 15, 3 weeks later) the pre-rTMS ratio is now lateralized to the left hemisphere. This reversal appears to happen at different times in the course of the treatment, thus for delta and alpha the reversal happens early after the first week of treatment (sessions 1-5). However, for beta 1 and beta 2, the reversal happens approximately towards the last week of treatment (sessions 11-15). This reversal of hemispheric asymmetry is obvious in all EEG frequencies except for the theta band where the pre- and post-values hit equilibrium at the end of the treatment. That is not to say that the trend towards complete reversal would never happen for theta, it may be that more treatment sessions are required for it to occur, or a larger sample size is needed. See figure 1 for an example of this for the alpha delta and Beta 2.1 frequencies.

With the full analysis, particularly the double-blind data, we hope to test whether these changes correlate with or even predict clinical response. Does the reversal of EEG hemispheric asymmetry indicate the turning point in their recovery to wellness? If so, then the different times at which the frequencies reversed their asymmetry raise fascinating questions about the relationship between the frequencies and their underlying neurophysiological mechanisms, and how this relates to the prognosis of depression. Can we use the degree of left hemispheric lateralization as an indicator of whether rTMS would be a successful therapeutic intervention for the patient? We will be able to address these changes once the study completes and the blind is lifted from the study. (December 2008).

DISCUSSION

A major limit of these data are that they are only collected from two prefrontal sites. This is however, the same montage as is being used in the EEG biomarker antidepressant trials, and is sufficient to show laterality changes. In fact, being able to predict responders using only 2 electrodes would be a significant advantage in a 'real-world' clinical setting. The combined EEG/rTMS methodology in MDD patients is the first study of its kind, and any information it yields potentially will be of vital importance as we continue to search for biomarkers and indicators of MDD and its treatment.

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DISCLOSURE AND CONFLICT OF INTEREST

Dr. George is a paid consultant to several brain stimulation companies and pharmaceutical companies. He is an unpaid consultant to three transcranial magnetic stimulation companies. He is a former paid consultant to Aspect Biomedical, an EEG manufacturer.

Dr. Funk is now a full-time employee of Pfizer, Inc. but was an employee of MUSC when she worked on this review.