Relationship between body mass and clinical response to repetitive transcranial magnetic stimulation (rTMS) for major depressive disorder

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) has been proven to be efficacious in the treatment of Major Depressive Disorder (MDD). We previously examined the effectiveness of rTMS for MDD in an applied clinical setting, AwakeningsKC Clinical Neuroscience Institute (CNI) and found high remission rates for patients diagnosed with MDD following rTMS treatment. An unexpected relationship with body composition and rTMS unit was discovered. This sub-study extends the previous investigation through a focused analysis of the effects of body composition on response to rTMS in the treatment of MDD. We utilized data collected from a retrospective review of medical records for patients diagnosed with MDD undergoing rTMS therapy at AwakeningsKC CNI. Patient Health Questionnaire 9 (PHQ-9) scores, time to remission status and body mass index (BMI) at baseline were considered while referencing two different rTMS instruments (MagVenture; NeuroStar). We found 23 (9%) of 247 participants met criteria for obese status (BMI≥30) with an average baseline PHQ-9 score of 22±4, classified as "severe depression". Obesity status was differentially impacted by the rTMS instrument used for treatment. Patients with obesity showed a shorter time to remission (mean 2.7±0.27 *vs*. mean 3.4±0.3 weeks) and proportionately greater remission rate (100% *vs.* 71%) when treated using the MagVenture relative to the NeuroStar instrument. Clinical response to rTMS therapy for MDD appears to be guided by individual factors including body composition and rTMS parameters such as the unit used for treatment. Further study of these influences could aid in the optimization of clinical response to rTMS.

Introduction

We previously examined Repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of major depressive disorder in an applied clinical setting (Awakening KC CNI) among varying populations and clinical variables.[1] The study involved the use of Patient Health Questionnaire 9 (PHQ9) scores and clinically defined remission rates based on changes in depressive symptomology being evaluated over a 6-week period. An overall remission rate of 72% was observed which was influenced by factors related to severity of psychiatric illness, substance abuse history, and surprisingly, the rTMS instrument utilized. In addition, the frequency of clinically rated remission was higher among patients meeting criteria for obesity.

Repetitive Transcranial Magnetic Stimulation (rTMS) is an approved treatment for Major Depressive Disorder as well as numerous other mental disorders.[2-5] The first TMS machine was developed in the 1980s, which targeted and influenced activity in the prefrontal brain regions and regulatory feedback pathways involved in depression, as a potential treatment for refractory depression.[6] The mechanism in which TMS works, involves a magnetic field being applied to the brain which induces changes in the electrical membrane potential and increases activity of the surrounding neurons.[7] It has been hypothesized that depression symptoms result from an abnormal level of neurotransmitter release leading to disruption of communication among select brain regions, such as the brain stem.[8] More specifically, the malfunctioning of the circuitry of some monoamine neurotransmitter, including serotonin, dopamine, and norepinephrine, has been linked to MDD. TMS treatment induces a magnetic field that acts as an electrical conductor, similar to neurons. The induced current has the power to evoke an action potential to help normalize chemical neurotransmission at the synapse, encourage regrowth of nervous tissue in the brain, changes in neurotransmitter systems, as well as excitability in the cortical regions of the brain. Obesity is associated with region-specific differences in gray matter volume corresponding with marked differences in the functional brain activation which could impact response to rTMS.[9,10] Reduced GM volume was identified in the "left inferior frontal gyrus, bilateral insula, left pyramis, inferior semi-lunar lobule and cerebellar tonsil, bilateral medial frontal gyrus, right anterior cingulate cortex, bilateral thalamus and left middle frontal gyrus".[11] In contrast, an increased grey matter volume was found in the "left inferior occipital gyrus and middle occipital gyrus than in the normal weight group".[11] The GM was also decreased in the limbic and cerebellum cortices, amygdala and pallidum. Reduced Anterior Cingulate Cortex (ACC) activation in obese individuals, as well as alterations in the insula, which is a part of the brain that underlies emotion processing, decision-making, and working memory. Widya *et al.*[12] (2011) observed that there was a larger amygdala in obese individuals *versus* non-obese individuals. There is a gap in literature regarding factors influencing the relative response rates for obese and non-obese patients and how they may influence rTMS treatment for MDD. The goal of this paper is to explore this unexpected observation and determine if there is support for its validity.

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Materials and Methods

AwakeningsKC Clinical Neuroscience Institute

AwakeningsKC CNI is a tertiary health care center for outpatient psychiatric treatment located in Prairie Village, Kansas. The center is Kansas State Certified for Cognitive Behavioral Therapy (CBT) with three clinics for Medication-Psychotherapy,

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repetitive Transcranial Magnetic Stimulation (rTMS), and intensive outpatient CBT. AwakeningsKC CNI has applied clinical data utilizing two similar rTMS stimulators, Mag Vita (MagVenture, Alpharetta, GA) and NeuroStar (Neuronetics, Malvern, PN).[13] Both instruments utilize a magnetic coil with a figure eight configuration but differ in several technical parameters such as coil composition and thermoregulation and pulse width of stimulation described in detail elsewhere.[14]

Data collection

This study was conducted under the authority of the University of Kansas Medical Center Office of Research Compliance who reviewed the study protocol and monitored study activities to ensure that appropriate steps were taken to protect the rights and welfare of humans participating as research subjects. Electronic medical records (Bestnotes, Twinfalls, ID) from patients of AwakeningsKC CNI were searched to identify adult men and women aged 18-80 years with Major Depressive Disorder who received up to 6 weeks of rTMS treatment as a component of their psychiatric treatment for depression. All study patients completed an 11-page downloadable assessment form prior to their initial visit. This form includes self-reported patient demographic information, detailed substance abuse history, psychiatric self-assessment, past psychiatric treatment, medical history, current and past medications, family medical history, and family psychiatric history. Changes in PHQ9 score and time to remission from depression for obese and non-obese individuals was assessed as the primary outcome with medical, psychiatric and family history and demographics including age, sex, education, socio-economic status, marital status, and employment evaluated as co-variates.

Data analysis

The data was analyzed using the SAS 9.2 version statistical software (SAS Institute Inc. Cary, North Carolina, USA). The baseline subject characteristics are presented in Table 1 with bivariate analysis using Chi Squared test and simple analysis of variance. PHQ9 scores were analyzed using repeated measures MANOVA controlling for TMS unit and obesity status. Time to remission from depression was examined using Logrank test stratified by obesity status and TMS unit (Table 2).

Results

We found 23 (9%) of 247 participants met criteria for obese status (BMI≥30) with an overall average baseline PHQ-9 score of 22±4, classified as "severe depression". As shown in Table 1, individuals with obesity were generally similar to non-obese individuals and did not differ by gender or by history of psychiatric hospitalization. Further, baseline PHQ9 scores were not correlated with BMI. Overall there was marked improvement with rTMS therapy for all participants as indicated by a significant decrease in PHQ9 scores shown in Figure 1. Figure 1 also shows an apparent differential response for obese individuals treated using the MagVenture instrument relative to other groups. This relationship was further supported by repeated measures regression modeling which showed a significant 3-way interaction between obesity status and rTMS instrument over time (Table 2). Obesity status was distinguished from BMI which did not directly correlate with PHQ9 outcomes.

Logrank test of time to remission from depression was examined for obese and non-obese patients while controlling for the effects of rTMS unit (Figure 2). All 15 Patients with obesity treated on the MagVenture instrument remitted by the 4th week of treatment in a mean of 2.7±0.27 weeks. This is compared to 5 of 7 individuals with obesity treated using the NeuroStar instrument after 6 weeks (mean 3.4±0.3 weeks to remission) further supporting a differential effect of rTMS unit on clinical response for individuals with obesity.

Discussion

Patients in our clinical sample meeting criteria for obesity showed a differential response to rTMS therapy exhibiting proportionally higher clinical remission rates in a shorter timeframe when treated using the MagVenture instrument than patients without obesity treated using the NeuroStar

Table 1. Baseline subject characteristics.

Variable	Obese (N=23) N (%) or Mean	Non-obese (N=224) N(%) or Mean	χ^2 or F	P-value
Male Gender	10 (43%)	88 (39%)	0.15	0.7
Age	44.1±14 years (19-66 yrs)	42.4±14 years (18-78 yrs)	F=0.4	0.52
Baseline PHQ9 Score	22.1±4 (9-27)	22.5±4 (14-30)	F=0.3	0.6
Prior Inpatient Psychiatric Hospitalization	14 (61%)	140 (62%)	0.02	0.88
TMS unit "M" *vs* "N"	7(30%)	92(42%)	1.1	0.28
Remission Rate at 6 weeks	20 (87%)	157 (70%)	2.9	*0.09*

Baseline demographic characteristics by obesity status with bivariate analyses using Analysis of Variance and Chi Squared test. P<0.05 indicates a statistically significant difference for individuals with obese status (BMI≥30) compared to non-obese status. Statistically significant trends are indicated in italics.

Table 2. The GLM Procedure for Repeated Measures Analysis of Variance Within Subjects Effects on PHQ9 Scores over 5 Weeks. Interaction Model of Obesity Status with TMS Unit.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Time	5	4003	801	67.0	*<.0001*
Time*Obese	5	16	3.1	0.26	0.93
Time*TMS Unit	5	261	52	4.4	*0.0007*
Time*Obese*TMS Unit	5	201	40	3.4	*0.0053*
Error(Time)	500	5971	12		

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instrument. This facilitated response was reflected in both decreased PHQ9 scores, proportion and time to clinical remission from MDD symptoms Obese and non-obese patients were otherwise similar and did not significantly differ in their baseline PHQ-9 scores, gender distribution or severity of psychiatric illness. We have previously reported differential effects of the two rTMS instruments, but there is no ready explanation for the relationship.[1] Qualitative differences in coil design or pulse width could lead to perceptible differences including pain more commonly reported for the NeuroStar instrument. It is possible that individual factors such as BMI might influence functional or structural parameters in the brain augmenting cellular signaling, neuronal activity or regional connectivity impacting clinical response. However, BMI was not directly related to PHQ9 scores suggesting the possibility of a threshold effect limited to high BMI.

Areas of the brain that differ between individuals with and without obesity include the gray matter, the ACC, orbital frontal corticostriatal (OFC) and the amygdala implicated in the pathophysiology of MDD which may play a role in rTMS response.[9,10] Past literature has also emphasized differences in serotonin levels in individuals living with binge eating disorder (BED), compared to individuals not diagnosed with BED.[15] Given the accompanying depression that can arise in individual diagnosed with BED, as well as the weight gain accompanying this disorder, it can be speculated that serotonin abnormalities could be a potential link between the variable of BMI, brain differences, and depression. Operational aspects of rTMS cortical excitability have been associated with physical conditioning with athletes showing lower resting motor thresholds compared to non-athletes.[16] But, cortical excitability measured with rTMS did not appear to be influenced by BMI above or below 25.[17] Additional factors such as water composition in the brain that may parallel body fat content could also affect neuronal excitability and rTMS response.[18,19] Electric and magnetic fields applied to pure water can induce persistent changes in the molecular properties of water (*e.g.*, increased Van der Waals forces, viscosity and altered solubility) which might influence sensitivity towards rTMS therapy.[20-23]

Limitations

This study was conducted in a real-world clinic, and was not a randomized, double blinded clinical trial, which increases the ecological and population validity of the findings. However, this also led to some limitations including potential bias in group designations, severity of illness, small sample size and reduced statistical power which limit the interpretation of study findings. There was also an intrinsic bias associated with the order of treatment since the NeuroStar instrument was purchased prior to the MagVenture.

Conclusions

Our investigation of obesity status predicting outcomes for depression yields a significantly higher remission rate for obese patients versus non-obese patients when

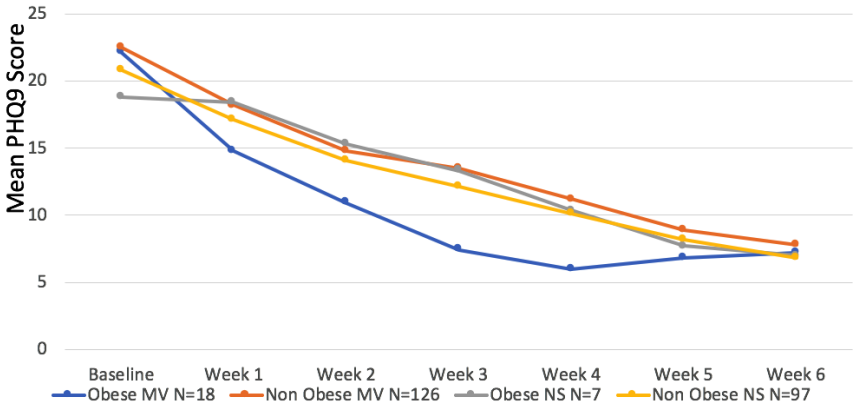

Figure 1. PHQ9 Scores for Obese and Normal Weight Patients with Major Depressive Disorder Treated using MagVenture or NeuroStar TMS Units. Repeated measures MANOVA of PHQ9 scores at week 5 for N=104 subjects showed a significant main effect of time (F=31.8, Num Df=5, Den Df=96, P<0.0001); a significant time*TMS Unit interaction effect (F=2.9, P<0.02) and a significant time*TMS Unit*obesity status effect (F=2.3, P<0.05). The interaction effects were lost at week 6. MV=MagVenture; NS=NeuroStar

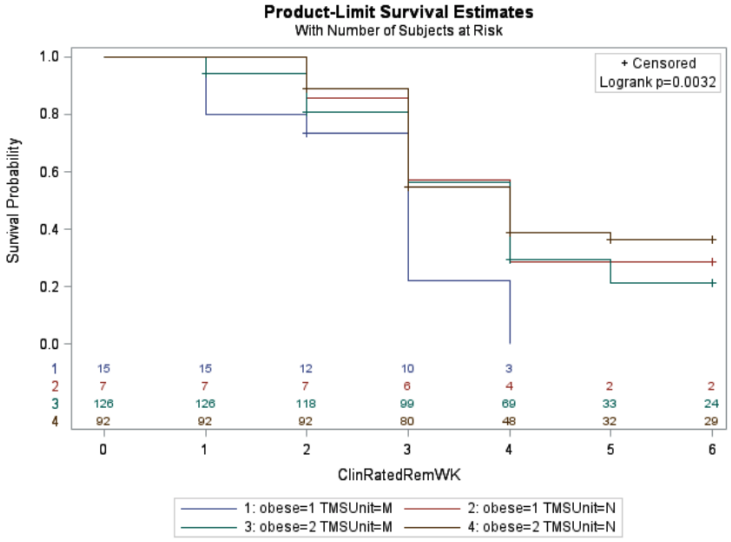

Figure 2. Time to Remission for Obese and Normal Weight Patients with Major Depressive Disorder Treated using MagVenture or Neurostar TMS Units. Logrank test of time to remission from depression for obesity status controlling for TMS unit showed higher remission rates for patients with obesity treated on the MagVenture TMS unit than those treated using the Neurostar unit. Legend indicates the four comparison groups with Obese 1 = Obese status, Obese 2 = Non-obese status, TMS Unit M=MagVenture and TMS Unit N= NeuroStar. The number of non-remitted patients are shown for each group at each time point.

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undergoing treatment using the MagVenture versus the NeuroStar rTMS instrument. This investigation adds to the literature base on rTMS and prompts further questions regarding the mechanism of action and factors contributing to individual differences in response.

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