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Fractional anisotropy (FA) changes after several weeks of daily left high frequency rTMS of the prefrontal cortex to treat major depression

F. Andrew Kozel, M.D., M.S.C.R.^{a,b,c}, Kevin A. Johnson, Ph.D.^{b,c}, Ziad Nahas, M.D., M.S.C.R.^{b,c}, Paul A. Nakonezny, Ph.D.^d, Paul S. Morgan, Ph.D.^{e,f}, Berry Anderson, B.S.N., R.N.^{b,c}, Samet Kose, M.D.^{b,c}, Xingbao Li, M.D.^{b,c}, Kelvin O. Lim, M.D.^g, Madhukar Trivedi, M.D.^a, and Mark S. George, M.D.^{b,c}

^aDepartment of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, USA

^bCenter for Advanced Imaging Research (CAIR), Medical University of South Carolina, Charleston, South Carolina, USA

^cBrain Stimulation Laboratory, Department of Psychiatry, Medical University of South Carolina, Charleston, South Carolina, USA

^dDepartment of Clinical Sciences, Division of Biostatistics, University of Texas Southwestern Medical Center, Dallas, Texas, USA

^eAcademic Radiology, University of Nottingham, Nottingham, NG7 2UH, UK

^fPhysics and Astronomy, University of South Carolina, Columbia, SC 29208

^gDepartment of Psychiatry, University of Minnesota, Minneapolis, MN

Abstract

Objectives—As part of a sham controlled treatment trial using daily left rTMS, brain changes associated with four to six weeks of treatment were examined using diffusion tensor imaging (DTI) in order to non-invasively evaluate prefrontal white matter microstructure. A decrease in fractional anisotropy (FA) values of the left prefrontal white matter could indicate damage to the region.

Methods—DTI was performed prior to and after 4–6 weeks of daily rTMS treatments. Mean FA levels associated with active rTMS and sham rTMS for the right and left prefrontal white matter (LPF-WM) were assessed.

Results—Adequate images were acquired for eight participants (active n=4, sham n=4) before and after rTMS. A mean increase was found for the LPF-WM. The mixed model revealed a trend toward a significant Treatment Group × Region interaction effect (p=0.11). Further, simple Region effects (left prefrontal WM vs. right prefrontal WM) were at a trend toward significance for

*Corresponding author: F. Andrew Kozel, M.D., M.S.C.R., Assistant Professor UT Southwestern Medical Center Department of Psychiatry 5323 Harry Hines Blvd. Dallas, TX 75390-9119, Phone: 1-214-648-0157, Fax: 1-214-648-0168, Andrew.Kozel@utsouthwestern.edu.

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difference after treatment within the active rTMS group ($p=.07$), but not within the sham rTMS group ($p=.88$).

Conclusions—RTMS resulted in no evidence of damage to WM on the side of stimulation. DTI may offer a unique modality to increase our understanding of mechanisms of action for rTMS.

Keywords

Diffusion Tensor Imaging (DTI); Transcranial Magnetic Stimulation; rTMS; depression; mixed linear model analysis of repeated measures

Introduction

Recent reports have highlighted that, although there are a number of effective treatments for depression, a significant portion of patients still fail to improve with standard medication therapies (1,2). New treatments are actively being investigated to treat this devastating syndrome. One promising modality is daily prefrontal repetitive transcranial magnetic stimulation or rTMS (3). Repetitive TMS involves using rapidly alternating current in a coil to induce magnetic fields. These magnetic fields pass from the coil relatively unimpeded to the brain and induce electrical fields. These electrical fields can depolarize neurons (e.g., stimulating the thumb area of the motor strip cortex can make the thumb twitch) (4). Daily prefrontal rTMS for at least 2 weeks has been found to have antidepressant properties when treating patients with depression (5–11). A multi-site industry supported treatment trial using left high frequency rTMS was recently conducted to see if active rTMS versus sham (placebo) rTMS produced a significantly greater treatment effect (12), and to potentially gain FDA approval of rTMS for depression. The Medical University of South Carolina (MUSC) was one of the participating sites in this trial. The data presented only represent those participants enrolled at MUSC.

One of the least understood aspects of TMS, however, is what brain changes occur with the treatment. One concern has been whether any destructive changes are associated with rTMS. Structural (13), diffusion imaging (14), and the combination (15) have provided support for the safety of the rTMS. One study did find brief changes in diffusion scans after a single rTMS session (16). They performed diffusion weighted imaging immediately before and after 12 minutes of 1Hz stimulation at 90% motor threshold over the motor cortex (MT – amount of energy required to move the first dorsal interosseus 50% of the time) (16). An initial decrease in apparent diffusion coefficient (ADC) was found in the region stimulated by the rTMS, but the effect was not detectable at five minutes. This was in contrast to the Li et al. 2003 study which found no such difference. All the diffusion studies to date, of which we are aware, have assessed the effects of a single TMS session.

Understanding the brain alterations associated with the positive clinical changes that occur with rTMS is also of significant interest. A number of studies have looked at functional changes using SPECT (17–24) and PET (3,25–27) that are associated with rTMS treatments. Metabolic changes have also been investigated with proton magnetic resonance spectroscopy (28). We are, however, unaware of any studies that have investigated white matter structural changes as a function of repeated daily rTMS treatments for depression.

Diffusion imaging, more specifically diffusion tensor imaging (DTI), has been used to investigate white matter microstructure (29). Specifically, fractional anisotropy (FA) has been found to be a sensitive measure of brain damage (30). Huisman et al. and Benson et al. both found FA values to be decreased in patients with traumatic brain injury and to be correlated with severity of illness scores (31,32). DTI also has been used to evaluate predictors of treatment response in patients taking antidepressants with late-life depression

(33), to evaluate the nature of white matter hyperintensities (34), to investigate schizophrenia (35), to model the area stimulated with TMS (36), and to investigate the effects of electroconvulsive therapy (ECT) on white matter (37). Nobuhara et al. scanned eight participants within two weeks before bilateral ECT treatments and at least 2 weeks post completion of the treatment course. In addition, twelve age-matched controls were scanned a single time. White matter FA values in the frontal regions in the group with depression were significantly reduced compared to controls prior to ECT. After ECT, however, there was a significant increase in prefrontal FA and the difference between the depressed group and controls disappeared.

The purpose of the current study was to investigate if brain changes measured with DTI occurred with several weeks of daily active rTMS versus sham rTMS. Although the prior imaging studies of single TMS sessions did not appear to produce any lasting changes as measured by diffusion scanning, we wondered if repeated daily rTMS stimulation over the course of weeks might cause any brain changes. We were interested in testing for damage as well as potential beneficial effects. A decrease in white matter FA values would indicate reduced white matter integrity, while conversely, an increase in FA values may indicate increased white matter integrity (29). In an exploratory manner, we investigated if active rTMS would result in significantly different FA values in the prefrontal white matter of the left hemisphere (the side stimulated with rTMS) compared to sham rTMS. We also examined whether values of FA in the prefrontal white matter would be significantly different in the left prefrontal white matter than in the right prefrontal white matter for the active rTMS group but not for the sham rTMS group.

Materials and Methods Participants

Participants included outpatients who were between 18 and 70 years of age and who were suffering from a mild to moderately resistant major depressive episode (HRSD-17 score ≥ 20 and Item 1 score ≥ 2 at screening; and HRSD-17 score ≥ 18 and $\leq 25\%$ decrease in HRSD-17 score at baseline) that was at least 4 weeks in duration, but not more than 3 years. Resistance to treatment was defined as ATHF level 2–4 in the current episode (38). If there were insufficient number of treatment trials in the current episode, then participants must have failed at least 1 trial and not more than 4 in a previous episode. Also, if participants were unable to reach adequate duration and dose due to intolerance, then they could be included if they experienced intolerance to greater than four antidepressant medications in the present or previous episodes while not meeting adequate ATHF criteria in the current episode. Participants were recruited from the Charleston community. Exclusionary criteria included: depression secondary to substances or medical condition; depression exhibiting a seasonal pattern; history of substance dependence or abuse within the past year; lifetime history of psychotic disorder, bipolar disorder or obsessive compulsive disorder; eating disorder or post-traumatic stress disorder in the last year; failure to respond to ECT in this or previous episodes; Mini Mental Exam Score (39) less than or equal to 24; as well as any history of neurologic (e.g., seizure disorder, stroke, cerebrovascular accident, etc.) or medical condition that would increase the risk of rTMS or MR scanning. All psychotropic medications were discontinued and prohibited except hypnotics (zaleplon, zolpidem, chloral hydrate, and/or zopiclone) for treatment emergent insomnia or lorazepam (up to 2 mg per day) for treatment emergent anxiety for up to 14 days immediately following randomization.

Repetitive TMS treatment

Participants were randomized to active or sham rTMS for 4–6 weeks, 5 days per week. The treatment parameters were high frequency (10 Hz) left prefrontal stimulation at 120% motor threshold for 75 trains of 4 second duration with an inter-train interval of 26 seconds (total

3,000 pulses per day). Those providing treatment, raters, and participants were blind to treatment allocation.

MRI scanning

Written informed consent approved by the MUSC Office of Research Integrity specifically for the neuroimaging was obtained from the participants where it was explicitly stated that their decision to participate in the imaging study would in no way impact their participation in the treatment trial. After signing the consent, participants were scheduled to be imaged immediately prior to the first rTMS treatment and then after they exited the acute portion of the sham controlled phase of the study (i.e. after daily rTMS was completed, but prior to being switch to open active treatment). This was at least 4 weeks, but could be extended to 6 weeks of daily rTMS treatments.

Participant's history and laboratory tests (i.e., pregnancy test) were checked to ensure that entering the MRI would be safe. The day of the scanning, participants were given a chance to practice the tasks and were made safe to enter the Philips 3.0 Tesla Intera MRI scanner. Participants had a structural scan, a DTI scan, 2 EPI functional tasks (simple motor and Sternberg working memory task), and a FLAIR image. The focus of this manuscript will be on the DTI scan. The six direction DTI scan (40) was 30 axial slices at 3mm using SENSE factor 2 (single shot Echoplanar Imaging, $b=1000 \text{ s/mm}^2$, TR 5000 ms, TE 100 ms, 90 degree flip angle, FOV 256 mm, matrix reconstruction 256 mm $\times$ 256mm).

Analysis of DTI images

The DTI images from the Philips MRI scanner were exported as PAR/REC files. The PAR/REC was converted to ANALYZE format using MRICro (<http://www.sph.sc.edu/comd/rorden/micro.html>). Analysis of the DTI was performed using FSL 3.3.5 (41) (<http://www.fmrib.ox.ac.uk/fsl/>).

Fractional anisotropy images from DTI—To create the Fractional Anisotropy (FA) maps, the DTI images were initially run with Eddy Correct in FDT (42). To create a brain mask for the DTI data, BET (43) was run on the DTI data using the initial B0 image. Using the DTI Fit function in FDT, the eddy corrected DTI images were analyzed using the structural brain mask and DTI acquisition parameters.

Prefrontal white matter masks—To create the prefrontal white matter masks, the participant's T-1 weighted structural was skull-stripped using BET. A six-direction rigid transformation of the skull-stripped T-1 weighted structural to the MNI reference image in FSL was performed using FLIRT (44). In order to segment the white matter, FAST (45) was run on the transformed-skull-stripped T-1 structural image. The three images created were inspected to determine which created image represented the white matter. For each participant, the coordinates of the rostral edge of the corpus callosum, the anterior commissure, and the midline were determined by FAK who was blind to treatment status. The left prefrontal white matter was defined as rostral to corpus callosum, dorsal to anterior commissure, and left of midline. The right prefrontal white matter was defined in the same manner except right of midline. Once the coordinates were determined, `avwmaths` in FSL was used to create the respective left and right prefrontal white matter mask.

Mean fractional anisotropy values for prefrontal white matter—To determine each participants mean FA values for the right and left prefrontal white matter, the individual subjects FA maps were co-registered to the masks using a 12 parameter affine registration in FLIRT. Using `avwmaths` and `avwstats`, the mean FA value was calculated for the regions corresponding to the left and right prefrontal white matter regions.

Statistical analysis

Our primary outcome measure was mean fractional anisotropy values associated with active rTMS and sham rTMS for the right and left prefrontal white matter. The primary data analysis was a 2 Treatment Group (active rTMS, sham rTMS) $\times$ 2 Region (left prefrontal, right prefrontal) mixed linear model analysis of repeated measures. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used, with the Kenward-Roger correction (46) applied to the unstructured covariance model. The baseline (pre-test) value of FA was included as a covariate in the mixed model analysis. The main effects of Treatment Group and Region and the Treatment Group $\times$ Region interaction effect were examined. Simple Treatment Group effects in each Region (left prefrontal white matter, right prefrontal white matter) as well as simple Region effects within each Treatment Group were also assessed. Cohen's *d* was calculated and interpreted as the effect size estimator for the between-subjects Treatment Group effect and the within-subjects Region effect. The level of significance was set at $p \leq .05$.

Results Participant characteristics

There were 14 participants who were randomized to active or sham rTMS at MUSC. All 14 agreed to participate in the imaging study and all had an initial imaging session. Three subjects discontinued the rTMS study and were therefore not imaged again. One subject was only able to tolerate the MRI long enough to acquire a structural scan. Two subjects did not have complete coverage of the dorsal aspect of the brain and were excluded. Thus, the fully imaged sample consisted of 8 participants (7 females). The age range was 29 to 59 years (with an average age of 44.6 years, $SD = 10.2$). The racial distribution included all (100 %) Caucasians. Two of the subjects receiving active treatment in our sample were responders and none of the participants receiving sham responded. Seven of the subjects were imaged prior to first rTMS treatment. Due to unavoidable scheduling issues, one participant was imaged 48 hours after first rTMS treatment. The subject was randomized to active. For post rTMS, subjects were imaged during the taper phase of the trial after their last rTMS treatment in the randomized portion of the trial. The time from last rTMS session to being imaged ranged from 2 to 128 hours ($M = 82.0$, $SD = 55.1$) hours for the group randomized to sham treatment and 1 to 48 hours ($M = 19.7$, $SD = 22.2$) for the group randomized to active treatment. The Wilcoxon two-sample test, using the *t* approximation with a one-tailed test, found no significant difference in time between the active and sham groups ($p = .11$). A nonparametric test was used here because of violation of the equality of variances assumption between the two groups on the scan time data.

The average pre-test FA value by treatment group and region was: active rTMS by left prefrontal white matter = 0.288 ($SD = 0.031$), sham rTMS by left prefrontal white matter = 0.281 ($SD = 0.036$), active rTMS by right prefrontal white matter = 0.268 ($SD = 0.011$), and sham rTMS by right prefrontal white matter = 0.254 ($SD = 0.019$). The active rTMS and sham rTMS groups did not differ statistically on any of these participant characteristics (p 's > 0.19). The participants' characteristics by group are reported in Table 1.

Fractional Anisotropy (FA)

The mixed model repeated measures analysis, for values of FA, revealed no significant Treatment Group effect ($F = .08$, $df = 1$, 4.98 , $p = 0.78$) and no significant Region effect ($F = 1.29$, $df = 1$, 6.68 , $p = 0.29$), but revealed a trend toward a significant Treatment Group $\times$ Region interaction effect ($F = 3.69$, $df = 1$, 4.94 , $p = 0.11$). Further, simple Region effects (left prefrontal white matter vs. right prefrontal white matter) also revealed a trend toward a significant difference on the adjusted mean post-rTMS FA values within the active rTMS group ($F = 4.71$, $df = 1$, 5.82 , $p = 0.07$), but not within the sham rTMS group ($F = .02$, $df =$

1, 6.40, $p = 0.88$). Simple Treatment Group effects were not significantly different in the left prefrontal white matter ($F = 1.22$, $df = 1$, 5.23, $p = 0.31$) or in the right prefrontal white matter ($F = .26$, $df = 1$, 5.45, $p = 0.63$).

The pattern of the adjusted least-squares means revealed that post-FA values were slightly higher for the active rTMS group than for the sham rTMS group in the left prefrontal white matter (0.283 vs. 0.274; $p < .31$; Cohen's $d = 0.72$), but not in the right prefrontal white matter (0.270 vs. 0.275; $p < .63$; Cohen's $d = -0.37$). Further, adjusted average values of post-FA were higher in the left prefrontal white matter than in the right prefrontal white matter for the active rTMS group (0.283 vs. 0.270; $p < .07$; Cohen's $d = 1.00$), but nearly identical in the left and right prefrontal white matter for the sham rTMS group (.274 vs. .275; $p < .88$; Cohen's $d = -0.08$). The results of the FA analyses, including effect sizes, are shown in Tables 2 and 3.

Discussion

We found that active rTMS resulted in greater post-rTMS treatment mean FA values in the prefrontal white matter of the left hemisphere (side stimulated with rTMS) compared to sham rTMS. The mixed model repeated measures analysis found a trend toward a significant treatment group (active v. sham) by region (left prefrontal white matter v. right prefrontal white matter) interaction effect ($p = .11$). The pattern of adjusted least squares means within the left PF revealed the post-FA values to be higher for the active rTMS group than for the sham rTMS group, with a moderate effect size (Cohen's $d = 0.72$). Mean FA values (adjusting for pre-rTMS values) in the prefrontal white matter were higher in the left prefrontal white matter than in the right prefrontal white matter for the active rTMS group at a trend level ($p = .07$; Cohen's $d = 1.00$), but not for the sham rTMS group ($p = .88$; Cohen's $d = -0.08$).

Importantly, the major finding was that no evidence of damage (reduction in FA values) was found in the region of the brain stimulated with rTMS. In addition, the resulting higher mean FA value in the left prefrontal white matter is intriguing. Although these values did not reach statistical significance, it is interesting to note that if the two subjects (one received active rTMS, one received sham rTMS) are included that were eliminated due to a small portion of the dorsal brain not imaged, the results of the mixed model revealed a significant Treatment Group $\times$ Region interaction effect ($p = 0.05$). Further, including these additional two subjects led to a statistically significant simple Region effect (left prefrontal white matter vs. right prefrontal white matter) after treatment within the active rTMS group ($p = 0.01$), but not within the sham rTMS group ($p = 0.60$).

One explanation for the selectively higher left versus right prefrontal white matter fractional anisotropy values after 4–6 weeks of treatment is that the daily repeated left prefrontal rTMS induced a positive effect on the white matter organization for the side of the brain stimulated. This might represent an improvement in structural integrity between the left dorsolateral prefrontal cortex and deeper limbic structures. Although at this stage of understanding FA values, there are other possibilities as well. Whether this also represents an increase in functional connectivity would require further study. These findings, however, raise the intriguing possibility that a mechanism of action of repeated daily rTMS may involve the structural connectivity between brain regions.

In accordance with the concept that rTMS may create structural changes as well as functional changes, May et al. found a significant increase in grey matter in the region of the brain stimulated with rTMS. (47) After 5 days of 1 Hz rTMS treatments at 110% motor threshold to the superior temporal gyrus, voxel based morphometry (VBM) of structural

scans found a significant increase in the grey matter of the region stimulated. Although these are different regions stimulated, using different TMS parameters, and a different imaging protocol, both support the idea that rTMS can induce structural as well as functional changes.

This study has a number of limitations that influences the appropriate interpretation of the findings. The small sample size with only four subjects in each group makes any conclusions very tenuous especially since the variability across time in FA values for people with depression is not known. Because of scheduling issues, we imaged one participant after receiving one rTMS treatment. This has the potential to confound our results. Because the subject was randomized to active, however, any confound would be expected to reduce a difference from baseline to end of treatment rather than enhance it. Also, a non-significant difference in time from prior rTMS treatment to post-treatment imaging was found between the active and sham group. The important point is that all scanning occurred greater than one hour from the time of prior rTMS treatment given Li et al. 2003 and Mottaghy et al. 2003 both reported no difference in diffusion measures after 5 minutes of rTMS from a single session. Future studies should nevertheless endeavor to avoid these two potential confounds.

Whether the difference seen is related to treatment response or just an effect of having rTMS applied is unclear. With 2 responders in the active group, the numbers were too small for any meaningful analysis of responders versus non-responders. We are gathering DTI data in the currently ongoing multi-site TMS depression trial sponsored by the NIH (called OPT-TMS) in order to address some of these issues.

Further work is needed with larger samples to test whether these results replicate and to address if increased values in the prefrontal white matter predict treatment response and at which point in treatment. If it is found that the changes in white matter FA values occur early and predict treatment response, these FA values could provide a clinically important metric in which to make treatment decisions regarding rTMS.

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Table 1

Participant Characteristics by Treatment Group

Participant Characteristic	Treatment Group		
	Active rTMS (n=4)	Sham rTMS (n = 4)	<i>p</i>
Age in years, M (SD)	39.7 (11.5)	49.5 (7.0)	0.19 ^a
Gender, N (%)			0.99 ^b
Female	4.0 (100)	3.0 (75.0)	
Male	0.0 (0.0)	1.0 (25.0)	
Pre-test MADRAS, M (SD)	29.2 (5.1)	29.5 (2.6)	0.93 ^a
Pre-test FA in left PF, M (SD)	.288 (.031)	.281 (.036)	0.79 ^a
Pre-test FA in right PF, M (SD)	.268 (.011)	.254 (.019)	0.24 ^a

^a *F* statistic was used to test for mean difference between the two treatment groups.

^b Fisher's exact test was used to test for differences between the two treatment groups.

M = Mean; SD = Standard Deviation; FA = Fractional Anisotropy; PF = Prefrontal Region

Table 2
Treatment Group simple effects by Region for mean levels of post-rTMS FA values

Region & Group	Levels of FA				
	<i>M</i>	<i>SD</i>	95% CI for <i>M</i>	<i>n</i>	<i>F</i> <i>p</i> <i>d</i>
Left PF & Group					
Active rTMS Group	0.283	0.013	0.267 to 0.299	4	
Sham rTMS Group	0.274	0.012	0.258 to 0.289	4	
Group Difference	0.009	0.013 ^a	-0.012 to 0.031	8	1.22 0.31 0.72
Right PF & Group					
Active rTMS Group	0.27	0.013	0.253 to 0.286	4	
Sham rTMS Group	0.275	0.014	0.257 to 0.292	4	
Group Difference	-0.005	0.014 ^a	-0.028 to 0.018	8	0.26 0.63 -0.37

Note:

M = Least Squares Means are adjusted for pre-test levels of FA;

SD = Standard Deviation;

95% CI = 95% Confidence Interval for expected mean value;

n = sample size.

Cohen's *d* = effect size estimator from modeled means and variance.

PF = Prefrontal Region

F statistic was used to test for mean differences in levels of FA between the two groups.

p = one-tailed *p* value.

Group difference = active rTMS mean value minus sham rTMS mean value.

^a pooled standard deviation.

Table 3
Region simple effects by Treatment Group for mean levels of post-rTMS FA values

Group & Region	Levels of FA				
	<i>M</i>	<i>SD</i>	95% CI for <i>M</i>	<i>n</i>	<i>F</i> <i>p</i> <i>d</i>
Active rTMS & PF					
Left PF	0.283	0.013	0.267 to 0.299	4	
Right PF	0.270	0.013	0.253 to 0.286	4	
Region Difference	0.013	0.013 ^a	−0.001 to 0.028	8	4.71 0.07 1.00
Sham rTMS & PF					
Left PF	0.274	0.012	0.258 to 0.289	4	
Right PF	0.275	0.014	0.257 to 0.292	4	
Region Difference	−0.001	0.013 ^a	−0.017 to 0.015	8	0.02 0.88 −0.08

Note:

M = Least Squares Means are adjusted for pre-test levels of FA;

SD = Standard Deviation;

95% CI = 95% Confidence Interval for expected mean value;

n = sample size.

Cohen's *d* = effect size estimator from modeled means and variance.

PF = Prefrontal Region

F statistic was used to test for mean differences in levels of FA between the two regions.

p = one-tailed *p* value.

Region difference = Left PF mean value minus Right PF mean value.

^a pooled standard deviation.