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Double-blind sham-controlled cross-over trial of repetitive transcranial magnetic stimulation for Mal de Debarquement Syndrome

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Abstract

Objective—To determine whether the chronic rocking dizziness that occurs in mal de débarquement syndrome (MdDS) can be suppressed with repetitive transcranial magnetic stimulation (rTMS) beyond the treatment period.

Methods—We performed a prospective randomized double-blind sham controlled cross-over trial of five-days of rTMS utilizing high frequency (10Hz) stimulation over the left dorsolateral prefrontal cortex (DLPFC).

Results—Eight right-handed women (44.5 (sd 7.0) years) with classical motion-triggered MdDS (mean duration 42.1 (sd 13.2) months) participated. Group level mixed effects repeated measures ANOVA showed improvement in our primary outcome measure, the Dizziness Handicap Inventory (DHI) at Post TMS Weeks 1, 3, and 4 ($p < 0.05$) and a trend at Week 2 ($p = 0.089$) after Real rTMS. On the Hospital Anxiety and Depression Scale, improvements started at Post TMS Week 2 for the Anxiety subscore and Post TMS Week 3 for the Depression subscore after Real rTMS only ($p < 0.05$). There were no group level improvements on the MdDS Balance Rating Scale after Real rTMS though there were three participants who improved on an individual level. There were no significant group level changes after Sham stimulation on any measure.

Conclusion—Our study provides evidence that the dizziness, mood and anxiety symptoms of MdDS can be improved with 10Hz rTMS over left DLPFC beyond the treatment period in selected individuals. rTMS may be a useful adjunctive treatment for the management of chronic rocking dizziness in individuals with MdDS but treatment durations longer than five days or maintenance treatment are likely needed for sustained symptom suppression.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) has been explored as adjunctive therapy in a widening group of medically refractory disorders that range from mood and anxiety, tinnitus, chronic pain, and stroke rehabilitation (1-5). However, there has been relatively little progress in exploring how it may be used to treat disorders of balance or motion

perception, despite balance disorders constituting a major and growing public health problem (6-9). Theoretically, neuromodulation could greatly impact motion perception and postural control owing to the widespread cortical projections of the vestibular system and its interrelationship with networks that are involved in cognitive and affective control (10,11).

A self-sustained disorder that occurs in the absence of any structural injury may be a useful model to study how neuromodulation affects self-motion perception. Individuals with *mal de débarquement syndrome* (MdDS) usually experience a low frequency rocking sensation that starts after they return to stable ground after water, air, or even land-based travel (12). These individuals are free from structural brain or inner ear disease and are otherwise physically healthy. Though the brief period of post-motion exposure rocking dizziness that occurs after travel is common among healthy young individuals, this post-motion rocking perception is persistent in MdDS (12). Individuals with MdDS typically feel better when they are back in motion again (e.g. getting back on the boat) indicating that the problem is one of maladaptive neuroplasticity due to entrainment to an oscillating background (13-15).

When this post-motion rocking dizziness becomes chronic, there are few treatment options; the longer the syndrome lasts, the less likely it is to spontaneously remit (14). Moreover, migraine and other headache types can develop in MdDS along with visual motion intolerance, fatigue and cognitive slowing (16, 17). Though medications like benzodiazepines and selective serotonin reuptake inhibitors (SSRI) can provide some symptom relief, they provide palliation rather than induce remission. Because of limited accessible treatment options, patients with MdDS experience high social burden, low quality of life, and high rates of depression (17, 18). Therefore, experimental neuromodulation offers a positive benefit-to-risk ratio from a treatment standpoint with a rationale supported by central metabolic, brain volume, and functional connectivity differences in MdDS compared to healthy controls (19-23).

Our first pilot study of rTMS in MdDS explored four protocols using the dorsolateral prefrontal cortex (DLPFC) as a neuromodulation target (24). In this study, 10 participants with persistent MdDS received one session each of high frequency (10Hz) or low frequency (1Hz) rTMS over the right or left DLPFCs. Acute decrease in the perception of rocking was most consistently observed after high-frequency (10Hz) stimulation over the DLPFC contralateral to the dominant hand. Pearce *et.al.* gave twice weekly 10Hz stimulation over the DLPFC contralateral to the dominant hand for four weeks (total of eight sessions) and showed improvement in objective balance function measured by the miniBEST scale and participant improvement measured by the Activities-specific Balance Confidence scale (25). Ding *et.al.* used a protocol using a combination of 1Hz right and 10Hz left DLPFC stimulation in right-handed participants led to improvement in five out of 10 participants with MdDS (26). These studies point to short-term efficacy of rTMS on rocking dizziness, but none have evaluated long-term improvement in MdDS symptoms with rTMS.

The following pilot study employed a double-blind sham controlled cross-over design of five days of left DLPFC 10Hz rTMS in individuals with MdDS with the goal of assessing whether improvement beyond the treatment period could be attained. We did not know the effect size of the long-term residual of multiple treatment sessions to calculate a sample size

a priori but we expected to see at least half of the participants experience some improvement given that seven out of 10 participants in the Cha 2013 pilot study experienced acute improvement after the 10Hz stimulation protocol (24). The participants were not asked to change any of their current medications but only to exhaust any medical options before enrolling in the study such as a course of physical therapy, a trial of an SSRI, and a trial of a benzodiazepine. The primary outcome measure was the Dizziness Handicap Inventory (DHI) (27) with secondary outcome measures being the Hospital Anxiety and Depression Scale (HADS) (28) and the MdDS Balance Rating Scale (MBRS). Narratives were elicited from the participants in order to assess effects that were not captured by these scales.

Materials and Methods

IRB and Consent

Study procedures were completed according to Declaration of Helsinki guidelines and were approved by the Institutional Review Board of the University of California Los Angeles, specifically Medical IRB 3, which oversees neuroscience research. Participants signed written informed consent. The original approval number for this study was 10-001273 with Clinical Trials identifier NCT02470377. This study utilized rTMS in an off-label manner.

Participant characteristics—Inclusion criteria were the following: 1) A chronic perception of rocking dizziness that started after disembarking from sea, air, or land based travel; 2) Symptoms lasting at least six months; 4) No other cause for symptoms after evaluation by a neurologist or otolaryngologist with appropriate testing for peripheral inner ear or other central nervous system cause for symptoms. Potential participants were excluded for the following: 1) Unstable medical or psychiatric condition (e.g. mania or psychosis), 2) Pregnant or planning to become pregnant during study enrollment, and 3) Contraindications to receiving rTMS or undergoing a structural MRI scan.

Seventeen potential participants were screened for the study and nine were excluded (CONSORT Diagram in **Supplemental Digital Content**). This resulted in eight right-handed women with a history of classical motion triggered MdDS participating in this pilot study (mean age of 44.5 (sd 7.0) years (range of 33 to 66 years); mean duration of symptoms of 42.1 (sd 13.2) months (range of 22 to 60 months). Specific triggers, current medications, and other MdDS related histories are listed on **Table 1**. All participants had normal screening neurological exams including head-impulse testing and each experienced temporary improvement of the rocking dizziness when back in motion, e.g. driving a car. Of note, no participant met criteria for vestibular migraine according to Appendix A1.6.6 of ICHD-3rd edition beta version (29).

Randomization—Both the Principal Investigator (PI) of the study and the participants were blinded to the treatment allocation until all study materials had been collected at the end of the study. The participants were randomly assigned to their allocation schedules by a third party not involved in the administration of TMS or data analysis and who only knew the participants by their initials.

The participants traveled to the research center for two one-week blocks, receiving five sessions of either Real or Sham rTMS during each block. After a two to four month wash out period determined by scheduling availability the participants were crossed to the other treatment arm without un-blinding. The rTMS treatments were administered by an experienced operator who was not involved in participant recruitment, had not previously met the participants, and had no knowledge of post-treatment effects.

MRI

Participants were scanned on a Siemens Magnetom Trio 3-Tesla scanner with a 12-channel head coil at the Ahmanson-Lovelace Brain Mapping Center (ALBMC). Specifications for Magnetization Prepared Rapid Acquisition Gradient Echo imaging were as follows: 192 slices at 1mm slice thickness, voxel size: 1.0mmx1.0mmx1.0mm, field of view: 256mm, flip angle: 9 degrees, repetition time=1900ms, echo time=3.25ms.

rTMS

rTMS treatments were administered at the ALBMC TMS Laboratory. rTMS was performed with the Magstim Rapid² stimulator with an airfilm-cooled figure-of-eight coil. Motor thresholds (MT) were determined before each individual session and were defined as the percent intensity output of the stimulator that generated a 50μV motor evoked response in the contralateral first dorsal interossei muscle 50% of trials. The Brainsight® frameless stereotaxy system was used for neuronavigation to aim for the left DLPFC in the middle frontal gyrus. rTMS was performed with the handle forward, 45 degrees off the mid-sagittal plane. After verification of the coil position with Brainsight®, each participant received 2000 pulses at 100% MT delivered as four-second trains at 10Hz (40 pulses) with a 26 second inter-train interval (50 trains). The participants received one session of rTMS each day for five consecutive days at the same time each day.

A dedicated sham coil that had the same appearance, weight, and sound as the Real rTMS coil was used for Sham sessions. In order to simulate the discomfort of Real rTMS, an electrode was placed on the Sham stimulator at the contact point with the participant's head. The electrical stimulations were timed with the rTMS pulses using a constant current stimulator (Digitimer, Ltd) triggered by the TMS machine through a BNC cable. The current intensity and duration of the stimulations were controlled manually to cause tolerable discomfort, which averaged about 4mA.

Symptom reporting

Participants began maintaining a diary one-week before each block of rTMS and for four weeks after the end of the week of stimulation. Therefore, they recorded a total of six weeks of questionnaires consisting of the DHI, the HADS, and the MBRS, which they completed once a week reflecting symptoms from the previous week.

The DHI is a well-validated 25-item scale of dizziness with a total possible score of 100 points in which a score of 16-34=mild handicap, 36-52= moderate handicap, and 54+=severe handicap (Jacobson & Newman, 1990). The HADS is a well-validated 14-item standard scale for measuring depression and anxiety with each subcomponent scoring a

maximum of 21-points in which a score of 0-7= normal, 8-10=borderline, and 11-21=abnormal. The MBRS (**Table 2**) is a 10-point scale adapted by the PI based a scale commonly used within the MdDS community (www.mddsfoundation.org). However, our scale solely assesses rocking perception and its effect on balance function rather than also incorporating cognitive components as in the MdDS Foundation scale. It is designed so that scores six and higher indicate impaired walking. The participants also wrote free entries in a paper diary that were turned in four weeks after each treatment block in a sealed envelope. These were reviewed at the completion of the study. The participants were interviewed by phone after each treatment block to assess any effects that were not captured by the questionnaires.

Statistical Analysis—Statistical analyses were performed with STATA IC version 14 (www.stata.com). Repeated measures mixed effects ANOVA analyses were performed for changes between baseline scores, the TMS week, and the four post treatment weeks for the DHI, the HADS, and the MBRS. The between-participant factor was the treatment allocation to Real or Sham rTMS and the within-participant factor was time. The data was fit with linear regression and a predictive model was created with a 95% confidence interval. Paired t-tests were also performed at each post-treatment time point for individual scores after Real vs Sham rTMS to determine whether there were individual differences in the average post rTMS treatment response. Since post rTMS scores were correlated and did not fulfill the criteria for independent measurements, a multiple-comparisons correction was not performed for post rTMS scores. Significance was defined as a two-tailed $p < 0.05$.

Results

All eight participants returned for the two week-long sessions of rTMS and completed all four weeks of post-rTMS diaries.

Dizziness Handicap Inventory

The change in DHI scores from baseline was compared between the Real and Sham stimulation weeks. **Figure 1A** shows decreases in the total DHI in Post TMS weeks 1, 3, and 4 ($p < 0.05$). There was a trend for improvement at Week 2 ($p = 0.089$) in the total DHI score. There were no significant improvements seen after Sham stimulation in the DHI.

Paired t-tests comparing the change in the DHI between each of the five post treatment time points between Real and Sham rTMS showed a significant difference on the group level for the DHI total score ($d.f. = 39$) (**Table 3**). Individual level changes are provided in **Supplemental Table 1** and DHI subcomponent graphs in **Supplemental Figure 1**.

MdDS Balance Rating Scale

Three individuals exhibited a favorable response to Real rTMS versus Sham rTMS (**Figure 1B, Supplemental Table 3**). However, one participant exhibited more improvement after Sham stimulation and two had scores worsen after Real stimulation but not after Sham stimulation. Therefore, on a group level there were no significant differences in MBRS scores between Real and Sham stimulation ($d.f. = 39$) (**Table 3**).

Hospital Anxiety and Depression Scale

Because the protocol used in this study is a shorter version of that used in the treatment of depression, changes in mood or anxiety symptoms were investigated over the course of the study. Group level Anxiety subscores significantly decreased starting at Post TMS Week 2 and Depression subscores decreased starting at Post TMS Week 3 for Real but not for Sham rTMS (d.f=39) (**Figure 1C and 1D**). Paired t-tests comparing changes in depression and anxiety scores across post rTMS time points showed a significantly greater improvement in both subscores after Real compared to Sham rTMS (**Table 3**). Individuals scores are provided in **Supplemental Table 3**).

Side effects

Seventy-seven of the possible 80 sessions were completed as two participants stopped prematurely (**Table 4**). These two participants felt that their rocking dizziness worsened during the course of one of the weeks of TMS so their sessions were stopped before all five were completed. After un-blinding, both of these treatment weeks were revealed to involve Sham stimulation. The most common side effect was head discomfort. Three participants consistently experienced some mild head tenderness over the stimulation site after both Real and Sham rTMS sessions but these resolved immediately or within minutes after the cessation of stimulation. One migraine headache with nausea and photosensitivity was triggered after Real rTMS in a participant with a history of migraine (Participant 2), but subsequent pretreatment with ibuprofen prevented migraine recurrences. There were two episodes of lightheadedness in two different participants, each occurring once.

Blinding

The participants guessed the correct allocation nine out of 18 times, which was three out of nine times after the first week and six out of nine times after the second week. The only reason that participants guessed that they had received Sham stimulation after the week of rTMS was because of no immediate treatment effects, whereas the main reason for guessing Real stimulation was because of perceived treatment intensity (**Table 4**).

Participant narratives

Participant narratives were obtained before un-blinding of the treatment allocation. Overall, four of the eight participants reported either moderate or significant improvement in their baseline function after one of the sessions of rTMS, all of which were revealed to be Real rTMS (**Table 4**). Even though the formal assessment period lasted for four weeks after each session of rTMS, continued communication with the participants revealed that Participants 1 and 2 experienced improvement for about three months and Participant 4 was still experiencing some improvement six months after Real rTMS. There was an equal distribution of participants with and without a history of migraine headaches amongst good and poor responders.

Discussion

Our study was designed as a double-blind sham controlled cross-over study in order to provide evidence of a long term effect of high frequency rTMS in the treatment of MdDS.

Though the sample size was small, the effect sizes were large enough that we were able to show that persistent clinically meaningful improvement in a medically refractory disorder of abnormal motion perception could be achieved with neuromodulation beyond the active treatment period. Improvements were seen on the group level in the DHI but not the MBRS, likely because the DHI has a larger dynamic range (100-points) than the MBRS (10-points) and queries other forms of dizziness besides rocking. Five days of rTMS is significantly less than the standard treatment for depression, however (20-30 sessions) (3) (30). Our study would suggest that future attempts at neuromodulation over DLPFC either provide more treatment sessions or combine rTMS with maintenance or adjunctive treatment. The magnitude of any treatment effects was also likely lowered because of the need for the participants to travel for this study since this disorder is unique in being induced by travel. Despite this, half of the participants experienced some sustained improvement with real rTMS, including those who flew home after the study.

Chronic rocking dizziness such as occurs with MdDS or chronic subjective dizziness is not amenable to typical treatments available to treat dizziness such as the use of vestibular suppressants or vestibular therapy (14, 31). Other forms of non-pharmacologic modulation of visual and vestibular pathways are being explored to induce suppression of the rocking sensation by un-yoking maladaptive vestibular-ocular reflex cross-coupling (32). Our present study as well as our other preliminary work shows that intervening on cortical areas that are part of or connected to circuits that cause perceptions of oscillation can be a promising therapeutic strategy (24) (26). Different types of motion perceptual disorders would theoretically require different cortical targets for modulation. For example, stimulation of specific brain areas during epilepsy surgical mapping such as the precuneus and the anterior cingulate cortex has been shown to induce an oscillating type of dizziness whereas actual hallucinations of rotation were more commonly induced with stimulation of the temporal lobe (33). Our study shows that the DLPFC may be one target for the treatment of rocking dizziness.

Limitations

There were several limitations to our study. First, we used a cross-over design in order for each participant to act as their own control. Because of the costs of travel to attend the study, we had to ensure that each participant would have had a chance to receive real therapy during the course of their participation and we wanted to treat the participants as equally as possible. However, a cross-over design risks introducing carry-over effects from one treatment session to the next. Although we tried to place a fairly long wash out period in between allocations (two to four months), we learned from this study that the effect of rTMS for rocking dizziness could last even beyond that range.

Second, the small sample size of the study was a limitation and may preclude generalizing to a larger audience. Our initial goal of determining whether any treatment effect would last beyond the treatment sessions was met, however. Moreover, even with only eight participants, we did see a range of treatment effects.

Finally, further travel can exacerbate the symptoms of MdDS and this was clearly a consideration in the study, which may have limited the therapeutic effectiveness on the

group level. This was a limitation of the study due to the rarity of the disorder. It was notable that two people had to stop their sessions mid-week during the Sham allocation because of worsened symptoms. Future therapeutic trials may need to use local resources or a home-based alternative in order to deal with the travel confound.

Conclusion

This study shows that even a short duration of treatment with high frequency rTMS over left DLPFC can induce longer-term changes in rocking dizziness in MdDS with side effects typically reported in other rTMS studies. Although the percentage of patients who improved was modest, our findings report a reasonable success rate for an otherwise intractable disorder with limited treatment options. Treatment for the chronic rocking dizziness of MdDS with rTMS may be a reasonable therapeutic option for some patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Change in the total score on the Dizziness Handicap Inventory (DHI) (A), Mal de Debarquement Balance Rating Scale, (B) and the Hospital Anxiety and Depression Scale, Depression (C) and Anxiety (D) subscores, relative to baseline immediately after Real (blue line) and Sham (red line) rTMS, and for four weeks after. Mixed-effects ANOVA with a linear model and 95% confidence interval for the mean predicted change at each time point was modeled for each score. Significant reductions in scores at $p < 0.05$ at each time point are noted with an “*,” which was only seen after Real rTMS.

Table 1

Participant Clinical History

Participant ID	Age at Study	Age at Onset	Duration (months)	Trigger	Medications taken during study	MdDS related history	Migraine history	Mode of travel to/from study
Participant 1	56	54	26	Flight	clonazepam, setraline, thyroid, bioidentical hormones	2 prior episodes: 1 after a flight (9 months); 1 after a cruise (4 months)	None	Drove ~6 hours
Participant 2	38	35	42	Amusement park ride	clonazepam, venlafaxine, thyroid, frovatriptan	1 prior episode after a cruise (2 months)	Migraine without aura	Flew West Coast <--->Midwest
Participant 3	47	42	52	Treadmill	none	1 prior episode after a cruise (1 month)	Menstrual migraines	Drove ~30min
Participant 4	33	30	44	Cruise	clonazepam, propranolol		None	Flew West Coast <--->East Coast
Participant 5	46	43	38	Cruise	clonazepam, verapamil		Menstrual migraines	Drove ~6 hours
Participant 6	45	39	60	Flight	none	3 prior episodes after flights (>3 weeks each)	None	Flew West Coast <--->Mountain
Participant 7	42	38	53	Boat/SCUBA diving	clonazepam prn, escitalopram, oral contraceptive		None	Flew West Coast <--->Mountain
Participant 8	49	47	22	Cruise	clonazepam, desvenlafaxine		Migraine with aura	Flew West Coast <--->Midwest

prn= as needed

Table 2**MdDS Balance Rating Scale**

1	No rocking.
2	Barely noticeable rocking. Walking is normal.
3	Mild intermittent rocking that can be easily ignored. Walking is normal.
4	Mild persistent rocking, which is distracting. Walking is normal.
5	Moderate intermittent rocking which requires extra attention to balance control. Walking is normal.
6	Moderate persistent rocking that leads to balance difficulty. May occasionally stumble.
7	Moderately severe but intermittent rocking that impairs walking. Needs occasional assistance to walk.
8	Moderately severe persistent rocking that leads to great balance difficulty. Needs assistance to walk for longer distances or specific situations.
9	Severe rocking causing great difficulty with walking. Needs constant gait assistance.
10	Severe rocking that prevents any walking.

Table 3

Group level differences in symptom score change

Score	Baseline-Real	Change Real	Baseline-Sham	Change Sham	<i>p</i> value	Favor
<i>DHI Total</i>	44.8 (17.3)	−9.8 (13.9)	40.0 (18.2)	−3.0 (9.1)	0.018	Real
<i>Functional</i>	16.0	−3.5 (5.8)	14.5	−1.4 (4.6)	0.129	Neither
<i>Physical</i>	13.5	−2.5 (4.7)	12.0	−0.2 (3.0)	0.006	Real
<i>Emotional</i>	15.3	−3.8 (4.7)	13.5	−1.5 (4.3)	0.021	Real
<i>MBRS</i>	3.9 (1.3)	0.06 (1.0)	3.5 (0.9)	0.4 (1.1)	0.133	Neither
<i>HADS-Depression</i>	7.1 (3.6)	−1.8 (3.3)	4.9 (2.6)	0.7 (2.9)	0.001	Real
<i>HADS-Anxiety</i>	6.6 (3.2)	−1.9 (2.2)	5.8 (4.1)	−0.5 (2.3)	0.004	Real

Table 4

Treatment allocation, side effects and participant narratives

Participant ID	Allocation	Guess	Reason for guess	Side effects	Participant narrative
First Allocation					
Participant 1	Sham	Sham	No change in symptoms	Mild headache and nausea once. Completed 4 of 5 sessions b/c of symptoms worsening.	No significant improvement after sham TMS.
Participant 2	Sham	Real	Able to use less clonazepam that week	Mild headache but severe fatigue	Became much worse after sham stimulation. Needed to nap everyday and increase baseline dose of venlafaxine and clonazepam.
Participant 3	Sham	Sham	No change in symptoms	None	No real change after sham TMS. Symptoms slightly worsened.
Participant 4	Real	Real	Rocking lessened with eyes closed	Mild headache	Initially experienced headache and increased visual motion sensitivity for about six weeks. This resolved. During that time, she also felt more stable when closing her eyes, however. Usual "ping-ponging" and body "sinking" sensation decreased. Energy and mood improved. Baseline clonazepam reduced.
Participant 5	Real	Sham	No change in symptoms	Mild headache. One episode of lightheadedness.	The usual "g-force" sensation she feels worsened after real TMS. Worsened headache was attributed to being premenstrual this week.
Participant 6	Real	Sham	No change in symptoms	None	No noticeable changes in symptoms after real TMS.
Participant 7	Sham	Real	Felt "something going through my brain"	None	Felt worse in the weeks after sham stimulation and needed to increase her baseline escitalopram dose, which did not help with her rocking dizziness but did help with visual motion intolerance.
Participant 8	Real	Sham	No change in symptoms	Mild headache	Symptoms were worse for about two months after real TMS, which was attributed to flying in for the study and undergoing a lot of stress at the time.
Second Allocation					
Participant 1	Real	Real	Felt more intense than prior visit	Mild headache	Significant functional improvement after real TMS, including decreased rocking perception, reduced visual motion intolerance, improved cognition, and improved mood. Able to return to the majority of her premorbid social and professional activities; nightly clonazepam was reduced to rare uses.
Participant 2	Real	Real	Felt more intense than prior visit	One episode of lightheadedness. Headache, fatigue, cognitive slowing.	Initially felt very tired after returning home following the week of TMS. Then, significant functional improvement followed, including almost no rocking perception. Balance improved enough to allow participation in a martial arts class. Cognitive "processing speed" improved. Migraine frequency declined. Daily clonazepam use decreased to occasional use.
Participant 3	Real	Real	Felt different than the prior visit	None	Baseline severity decreased gradually. Several weeks after TMS she experienced three days of no rocking dizziness. The rocking returned but severity scores were lower.

Participant ID	Allocation	Guess	Reason for guess	Side effects	Participant narrative
Participant 4	Sham	Sham	No change in symptoms	Mild headache	No significant changes after sham stimulation, but the improvement after the previous real TMS had carried over into this session.
Participant 5	Sham	Sham	No change in symptoms	None	No real change after sham stimulation. She was premenstrual the week before sham TMS so she had a pseudo-improvement of her symptoms, i.e. scores went down after sham stimulation because of her returning to baseline.
Participant 6	Sham	Real	Felt better that week	None	Did not experience any functional improvement.
Participant 7	Real	Real	Hurt more than prior visit	None	No noticeable change except for a temporary exacerbation of symptoms after traveling home.
Participant 8	Sham	Real	Symptoms worsened	Completed 3 of 5 sessions b/c of symptoms worsening	Much worse for at least eight months after sham TMS, again attributed to the stress of travel and circumstances.