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Repetitive Transcranial Magnetic Stimulation for Apathy in Mild Cognitive Impairment: A Double-Blind, Randomized, Sham-Controlled, Cross-over Pilot Study

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Abstract

Apathy is a common and disabling behavioral concomitant of many neurodegenerative conditions. The presence of apathy with Mild Cognitive Impairment (MCI) is linked with heightened rates of conversion to Alzheimer's disease. Improving apathy may slow the neurodegenerative process. The objective was to establish the efficacy of repetitive transcranial magnetic stimulation (rTMS) in improving apathy in older adults with MCI. An 8-week, double-blind, randomized, sham-controlled cross-over study was conducted in nine subjects (66 ± 9 years) with apathy and MCI. Subjects were randomized to rTMS or sham treatment (5 days/week) for 2 weeks following which they underwent a 4-week treatment-free period. Subjects then crossed-over to receive the other treatment for 2 weeks. The primary (apathy (AES-C)) and secondary (cognition (3MS & MMSE), executive function (TMT-A & TMT-B), and clinical global impression (CGI)) outcomes were assessed at baseline, 2, 6, and 8 weeks. After adjusting for baseline, there was a significantly greater improvement in the AES-C with rTMS compared to sham treatment at 2 weeks. There was

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significantly greater improvement in 3MS, MMSE, TMT-A, and CGI-I with rTMS compared to the sham treatment. This study establishes that rTMS is efficacious in improving apathy in subjects with MCI.

Keywords

rTMS; apathy; dementia; mild cognitive impairment; behavioral problems of dementia

1. INTRODUCTION

Over five million Americans have Alzheimer's disease (AD) and the lack of effective treatments has prompted research on prevention of dementia. Mild cognitive impairment (MCI), a prodrome of dementia is an attractive target for dementia prevention studies. The prevalence of MCI increases with age ranging from 16–20% among those aged 60 years and older and 29% in those aged 85 years or older (Lopez et al., 2003; Roberts and Knopman, 2013). The rates of conversion of MCI to AD vary from 10 to 30% annually (Morris and Cummings, 2005; Petersen et al., 1999). Given the wide range of AD conversion, research has focused on phenotypes of MCI known for higher rates of conversion to AD. The presence of behavioral problems increases the rate of conversion to AD. One key behavioral problem tipping the trajectory of neurodegeneration is apathy.

Apathy is a common and disabling behavioral concomitant of neurodegeneration such as Mild Cognitive Impairment (MCI) and Dementia. Apathy refers to a disorder of behavioral initiation or intention that can manifest in different ways like retarded emotional expression but not depression, and the failure to initiate a range of behaviors related to activities of daily living (ADL), that can be performed but are not initiated by the patient (Marin, 1991a). Although, there is some overlap with depressive symptoms, several groups have established apathy as a distinct entity lacking symptoms of dysphoria, suicidal ideation, self-criticism, feelings of guilt, and hopelessness (Levy et al., 1998). The prevalence of apathy in MCI has been reported to be as high as 60.5% (Ellison et al., 2008; Hwang et al., 2004; Lyketsos et al., 2002; van der Linde et al., 2016). Apathy appears early during MCI, increases in severity as the disease progresses, and tends to have a chronic course. In a population based study of older adults followed over ten years (N=3626), apathy was noted to be highly prevalent at 31.9%; and symptoms persisted for at least one year in 62% of subjects with apathy (van der Linde et al., 2016). Furthermore, the mortality rate among those with apathy was 3.1 times higher compared to those without apathy (van der Linde et al., 2016). Presence of apathy leads to rapid progression of symptoms and up to seven-fold rate of conversion to AD (Palmer et al., 2010). Thus, treatment of apathy in MCI has the potential to influence the trajectory of neurodegeneration.

Pharmacological treatment options for apathy are limited and may not be tolerated by many patients. Medications currently approved for AD have had mixed results in treating apathy; while cholinesterase inhibitors were effective in improving apathy in secondary analyses, memantine failed to do so (Cummings et al., 2015; Zhang et al., 2015). Modest improvements in apathy and cognitive correlates have been noted with dopaminergic agents

such as methylphenidate (Padala et al., 2017; Herrmann et al., 2008; Padala et al., 2010; Rosenberg et al., 2013). Our group has found that the best outcomes of apathy with methylphenidate were after 12 weeks of treatment and some domains of apathy such as novelty seeking and persistence still did not respond (Padala et al., 2017). Furthermore, stimulants may not be suitable for those with polypharmacy, and cardiac abnormalities. A recent review of available pharmacological treatments for apathy concluded that they have limited effectiveness, are expensive, and sometimes induce prohibitive side effects (Rea et al., 2014). Therefore, alternative or complementary adjuvant therapeutic strategies need to be explored. Repetitive Transcranial Magnetic Stimulation (rTMS), a noninvasive brain stimulation tool, is a potential therapeutic tool for apathy in MCI that might lead to rapid improvement in apathy and in signs and symptoms seemingly unresponsive to pharmacological treatments. Thus, the primary objective of our study was to establish the feasibility and efficacy of repetitive transcranial magnetic stimulation (rTMS) to improve apathy in older adults with MCI.

2. METHODS

2.1. Study design and participation:

This pilot study was a single site, double blind, randomized, sham-controlled, cross-over study of daily rTMS treatments five-times per week (20 sessions) with 4-weeks of treatment-free period between the interventions. The study was conducted at a Department of Veterans Affairs Medical Center. The protocol was approved by the Institutional Review Board of the Central Arkansas Veterans Healthcare System. Subjects were recruited via advertisements in clinical areas and referral from providers. All subjects were pre-screened by medical records review. Those who cleared the pre-screening were invited for the baseline visit. At the baseline visit, all subjects underwent UCSD Brief Assessment of Capacity to Consent (UBACC) (Jeste et al., 2007) screening. If the subjects scored 15 or higher on the UBACC scale, they were deemed to have capacity to consent and provided a written informed consent. If not, their caregivers provided written informed consent. Additionally, all caregivers provided written consent for their participation. Subjects underwent further screening for eligibility including a medical history and physical examination, and tests for apathy and memory. Subjects aged ≥ 55 years, who met Petersen's criteria for mild cognitive impairment, scored 30 or higher on the apathy evaluation scale-clinician version (AES-C), scored 23 or higher on the Mini Mental Status Examination (MMSE), cleared the TMS adult safety scale (TASS), and were on stable dose of antidepressants (if applicable) for at least two months prior to the enrollment were included in the study. Subjects receiving medications known to increase the risk of seizures or ototoxicity, or who had a history of bipolar disorder, seizure disorder, seizure disorder in first degree relatives, implanted device, stroke, aneurysm, or cranial neurosurgery, or a concurrent diagnosis of alcohol-related problems or current episode of Major Depression Disorder were excluded. Once eligibility was established, demographic and anthropometric data were collected. All primary and secondary outcome measures were assessed. After all baseline assessments were completed, subjects were randomized to the active-coil or the sham-coil treatments using a double-blind random block design developed by a statistician to ensure equal allocation to the cross-over order.

2.2. Intervention:

NeuroStar® TMS Therapy System along with the NeuroStar XPLOR system consisting of a XPLOR standard treatment coil, a blinded active-coil, a blinded sham-coil, a quick release hub, enhanced coil connector, coil cart, and the acoustic blinding hardware were used (Neuronetics, Inc., Malvern, PA). The XPLOR blinded active-coil is identical in appearance and function to the NeuroStar TMS Therapy System treatment active-coil except for a “coil type” label, “X” and “Y”. During XPLOR TMS treatment, the blinded sham-coil produces an equivalent sound intensity to the blinded active-coil but does not produce a therapeutic magnetic field. The acoustic blinding hardware disguises the acoustic tones of the blinded XPLOR coils. All subjects used foam earplugs with a noise reduction rating of 33dB (3M E-A-Rsoft SuperFit) and were not allowed to sleep during treatments.

2.3. Motor Threshold (MT) determination and treatment:

Single pulse TMS was used to find the scalp position of lowest MT for the right first dorsal interosseous or abductor pollicis brevis muscle using a pre-programmed algorithm in the NeuroStar device. The stimulation site was the left dorsolateral prefrontal cortex (DLPFC) defined as a location 5.5 cm anterior to the MT location. Three thousand pulses at 10Hz, 4-s train duration, and 26-s inter-train interval at 120% MT were delivered per session five times a week using the coil to which the subject was randomized. These parameters are within the published safety guidelines and are in keeping with depression treatment protocols (George, 2010; Rossi et al., 2009). Certified technicians, who were not raters, delivered the treatments. Each session lasted for about 45 minutes including time for set up and 37.5 minutes of stimulation. Adverse events were assessed at each visit by structured questionnaire and/or spontaneous complaints by patients and caregivers.

After 10 treatments, outcomes were assessed at 2-week visit (end of first treatment). Subjects then underwent a 4-week treatment-free period. The rationale for a 4-week treatment-free period was to allow subjects to return to baseline prior to the next treatment phase. In a systematic review and meta-analysis, the antidepressant effects of rTMS persisted for 1–2 weeks after discontinuation of rTMS in patients not taking any antidepressants and the stimulation parameters used in this study are similar to those used in treatment studies of depression (Lam et al., 2008). At the end of treatment-free period (6-week visit), the primary and secondary outcome measures were assessed (second baseline, beginning of second treatment). Subjects then received 10 treatments of the other coil and were assessed for primary and secondary outcomes at 8-week visit (end of second treatment). A final assessment was done at 12-week visit (after four weeks of no-treatment).

2.4. Outcome measures:

The primary outcome measure was the Apathy Evaluation Scale-Clinician version (AES-C). The secondary outcome measures included the Modified Mini Mental State Exam (3MS), Mini Mental State Exam (MMSE), Trial Making Tests- A and B (TMT-A&B), TMT-B errors, the Executive Interview (EXIT-25), Instrumental Activities of Daily Living (IADL), Activities of Daily Living (ADL), Clinical Global Impression - improvement (CGI-I), and Clinical Global Impression - severity (CGI-S) and Zarit Burden Scale (ZBS). All outcome measures were assessed by blinded raters.

2.4.1. Apathy: The AES-C is a measure of behavioral, cognitive, and emotional domains of apathy for the previous four-week period. A semi-structured interview is conducted to obtain information from the patient and caregiver. Scores range from 18 to 72 with higher scores reflecting more severe apathy. A score of 30 or higher is considered clinically significant apathy. AES-C has good internal consistency (Cronbach's $\alpha > 0.86$), and test-retest reliability (Pearson's $r > 0.76$) (Marin et al., 1991b).

2.4.2. Cognition: The 3MS is a global screen for cognition expanded from the MMSE and included tests for a broader range of cognitive capacity and difficulty levels (Teng and Chui, 1987). Scores range from 30 to100 to provide finer discrimination. The 3MS is known to be superior to MMSE as a community screen for dementia (McDowell et al., 1997). MMSE scores were derived from 3MS (Teng and Chui, 1987). Alternate word sets were used for recall since learning effects can have the most impact on results of the MMSE and 3MS scores.

2.4.3. Executive function: Executive function was measured with TMT-A, TMT-B and Exit-25. TMT-A&B are widely used tests for assessment of executive function (EF), and TMT-B test can differentiate apathetic patients from non-apathetic AD patients (Corrigan and Hinkeldey, 1987; Starkstein et al., 1997). EXIT-25 is a bedside measure of EF. It defines the behavioral sequelae of executive dyscontrol and provides a standardized clinical encounter for patient observation. It has 25 items and high inter-rater reliability (Pearson's $r = 0.90$) (Royall et al., 1992). Scores range from 0 to 50. The EXIT-25 has been used to detect executive dysfunction in MCI and AD.

2.4.4. Functional status: IADL were quantitated using a well-validated instrument that assesses eight domains of higher functions necessary to live independently such as ability to use telephone, shop, manage own medications, and finances etc. Scores range from 0 to 23 (Lawton and Brody, 1969).

2.4.5. CGI: The CGI is an observational scale of global evaluation, which assesses the change in degree of illness in relation to the original assessment (Guy W, 2016). Two components are used to assess overall clinical severity (CGI-S) and improvement (CGI I), each with a seven-point scale. At intake, only severity can be rated. In subsequent assessments, both severity and improvement were rated.

2.4.6. Caregiver burden: The ZBS is a widely-used 22-item assessment of the caregiver's burden related to patient relationship, physical and mental health, finances, and social life. Caregivers rate items from 0 (never) to 4 (nearly always) and higher scores indicate higher burden. It has excellent reliability (Zarit et al., 1980).

2.5. Statistical analysis:

Descriptive statistics for demographics and baseline cognitive measures were compared according to randomized group using the two-sample *t*-test or nonparametric Mann–Whitney test for continuous data or Fisher's exact test for categorical data. Given the cross-over design, changes in apathy score from baseline at weeks 2 and 8 (primary endpoint) were

analyzed using a mixed model analysis of covariance with fixed effects for treatment (rTMS or sham), sequence (rTMS first or sham first), and time (week 2 or 8). Baseline measurements of the outcome (at week 0 for 2-week outcomes and at week 6 for 8-week outcomes) were included as a covariate. A random subject effect was included to account for the correlation arising from repeated measurements on the same subject. A similar approach was used to analyze other cognitive measures, and a repeated measures logistic model (generalized estimating equations) was used to analyze binary outcomes. The study team, including the statistician, were unblinded to treatment assignment after all analyses were completed. A random subject effect was included to account for the correlation arising from repeated measurements on the same subject. Similarly, a repeated measures logistic model (generalized estimating equations approach) was used to analyze binary outcomes. Two-sided p-values less than 0.05 indicated statistical significance. Data were analyzed using SAS Enterprise Guide v5.1 (SAS, Cary, SC).

3. RESULTS

The screening, enrollment, and participation process is depicted in Figure 1. A total of 79 patients were screened to randomize nine subjects. Mean (SD) age of the subjects was 65.6 (9.3) years, four were Caucasian and five African American, and one subject was female. Four subjects were randomized to receive the active-coil treatment first, and five subjects to receive the sham-coil treatment first. One subject randomized to the active-coil treatment was withdrawn after the baseline visit, as he was unable to tolerate the treatment. Thus, there were three subjects in the active-sham arm who received the active-coil treatment first followed by sham-coil treatment, and five subjects in the sham-active arm (Figure 1). At baseline, there were no significant differences between the two arms with regard to age, gender, ethnicity, education, concomitant medications, and comorbidities (Table 1). There was significant difference in AES-C scores in the active-sham arm compared to sham-active arm at baseline ($t_{(7)}=-2.70$; $p=0.031$) (Table 2), and at 6-weeks, second baseline at the beginning of second treatment ($t_{(6)}=-2.92$; $p=0.027$).

3.1. Primary outcome, apathy:

For the eight subjects who completed the study, there was a significant between-group difference [average between-group difference (95% CI)] in the change in AES-C scores for active-coil treatment compared with the sham-coil treatment [−5.9 (−11.6 to −0.2), $t_{(5)}=-2.66$; ($p=0.045$)] (Table 3). Within-group analysis showed significant improvement in AES with the active-coil treatment ($t_{(5)}=-4.19$; $p=0.009$) and no improvement with the sham-coil treatment ($t_{(5)}=-0.82$; $p=0.450$). AES-C scores decreased in all subjects after receiving the active-coil treatment and both decreased and increased after receiving the sham-coil treatment. The mean improvement of AES-C score in the active-coil treatment group was 7.4 points. A change greater than equal to 3.3 points on AES-C is generally considered clinically significant (Lanctot et al., 2014).

3.2. Secondary outcome measures:

There was a significant between-group improvement in 3MS favoring the active-coil treatment [5.2 (1.2 to 9.2), $t_{(5)}=3.34$; ($p=0.021$)] (Table 3). Within-group analysis showed

significant improvement in 3MS with the active-coil treatment ($t_{(5)}$=4.65; p=0.006) and no improvement with the sham-coil treatment ($t_{(5)}$=−0.19; p=0.860). There was a significant between-group improvement in MMSE favoring the active-coil treatment [3.4 (1.9 to 5.0), $t_{(5)}$=5.75; p=0.002] (Table 3). Within-group analysis showed significant improvement in MMSE with the active-coil treatment ($t_{(5)}$=5.59; p=0.003) and no improvement with the sham-coil treatment ($t_{(5)}$=−1.05; p=0.340). There was a significant between-group improvement in CGI-I favoring the active-coil treatment [−2.5 (−3.8 to −1.1), $t_{(5)}$=−4.76; p=0.005] (Table 3). For the CGI severity, the odds of the score being normal to mild (best 3 categories) was 7.0 times higher for the active-coil treatment as compared to the sham-coil treatment (OR, 7.0, 95% CI, 0.9–53.2; Z=1.88; p=0.060). There was a significant between-group improvement in TMT-A favoring active-coil treatment [−4.6 (−8.8 to −0.3); $t_{(5)}$= −2.74; p=0.041]. There were no significant between-group or within-group differences for any of the other secondary outcomes (Table 3).

3.3. Adverse events:

There were 16 adverse events experienced by 9 subjects, all of which resolved without sequelae. Most adverse events were experienced while receiving rTMS (14 events in 8 subjects) compared to only 2 events with sham treatment (neck discomfort and ER visit for unrelated wrist pain). The most common adverse event was discomfort at the treatment site (8 events in 6 subjects) with 4 subjects rating the discomfort as mild, 1 as moderate, and 1 as severe. In all cases the coil placement was changed and/or the magnet strength reduced, and one subject who experienced severe pain with 2 treatments was discontinued from the study. The remaining adverse events related to rTMS were shock sensation at treatment site (n=1) or to eye (2 events in 1 subject), facial twitching (n=1), insomnia (n=1), and dizziness upon standing (n=1); all of which were mild.

4. DISCUSSION

The main objective of the study was to compare the effects of rTMS to sham treatment on apathy in those with MCI. There was a significantly greater improvement in apathy scores after 10 rTMS treatment sessions compared to an equal number of sham treatments. Enhanced dopamine transmission in the prefrontal cortex, the ipsilateral anterior cingulate, and medial orbitofrontal cortex with left DLPFC high frequency rTMS, as detected in prior studies, could explain the improvement in apathy seen in the current study (Cho and Strafella, 2009). This is a significantly faster improvement of apathy compared to what has been demonstrated with pharmacological treatments. The most robust evidence of pharmacological treatment of apathy is with methylphenidate. In three RCTs of methylphenidate, the best improvement of apathy was realized after twelve weeks of treatment (Herrmann et al., 2008; Padala et al., 2010; Padala et al., 2017; Rosenberg et al., 2013). Furthermore, apathy improved in all subjects after the active-coil treatment but improved in some and worsened in others after the sham-coil treatment, highly suggestive of rTMS as a new non-pharmacological venue for treatment of apathy. This finding is particularly salient, as non-pharmacological treatments for apathy are limited. An RCT of left DLPFC anodal transcranial direct current stimulation (tDCS) in patients with moderate AD (N=40) failed to show improvement in apathy (Suemoto et al., 2014). Similarly, a recent

review of nonpharmacological treatments of apathy found mixed results with individualized cognitive rehabilitation, multi-sensory stimulation, and tailored activity programs and that randomized controlled trials were lacking (Theleritis et al., 2017). Thus, there is an urgent need for non-pharmacological treatments for apathy and the current study adds a potential tool for non-pharmacological treatment of apathy.

rTMS may be a good fit for apathy treatment as frontal lobe dysfunction is implicated in the etiology of apathy. Several lines of evidence suggest that apathy is characterized by decreased activity in prefrontal sub-cortical circuits. Neurophysiological and neuroimaging studies of apathy have demonstrated abnormal activity in DLPFC, orbitofrontal cortex (OFC), medial prefrontal cortices (MPFC), anterior cingulate gyrus, and supplementary motor area (SMA) (Benoit et al., 2004; Robert et al., 2006; Sultzer DL et al., 2013). Furthermore, a hypodopaminergic state in the reward circuitry leads to apathy, and dopaminergic agents reverse apathy. Since high frequency rTMS over the left DLPFC is known to have an additional, propagated, intermediate effect of enhancing dopamine transmission in the prefrontal cortex, the ipsilateral anterior cingulate, and medial orbitofrontal cortex, rTMS could serve as a treatment for apathy (Pogarell et al., 2007; Pogarell et al., 2006). Significant improvement was also noted in global screening tools of cognition. Improved synaptic plasticity induced by long term potentiation is seen with multiple sessions of high frequency rTMS explaining its cognitive benefits (Hoogendam et al., 2010; Siebner et al., 2009). These results are consistent with pilot studies of rTMS for cognition in MCI (Sole-Padulles et al., 2006).

Although there are no studies in apathy using rTMS, comparable studies are available for negative symptoms of schizophrenia and depression. A recent meta-analysis found heterogeneity in the stimulation parameters and site of stimulation (Dlabac-de Lange et al., 2010). However, after a careful evaluation, authors found that stimulation at 10Hz on the left DLPFC produced the best effect size and has been the most replicated treatment of negative symptoms of schizophrenia (Dlabac-de Lange et al., 2010). Apathy is one of the subgroups of the negative symptoms that improves consistently with rTMS treatment (Prikryl et al., 2013). Another implication of the area of research is the promise of using the intervention in those currently being treated with antipsychotics for whom the use of stimulants would be contraindicated.

Sample size is a limitation of the study; however, the crossover design offers greater statistical power in this study. Another limitation was that the subjects were predominantly male which limits generalization to females. There was also a significant difference in the AES between those assigned to the active-sham arm and the sham-active-arm despite randomization which was controlled by adjusting for baseline. The change in AES was calculated after adjusting for baseline, thereby increasing the precision of the treatment effect estimate. Stratification during randomization would have decreased this risk. Although patients with current episode of major depressive disorder were excluded from participation, and the dose of antidepressants (if applicable) was required to be constant over the previous two months, it is possible that some of the improvements could be a result of improvement in residual depression which was not quantitated in the study. Larger studies would need to systematically measure depression, and control for the change in depression scores and

antidepressant treatment in the post-hoc analyses. We also acknowledge that this is a pilot study and that the patients were preselected for apathy rather than selected at random from a larger pool.

The major strength of the study is its study design, a double-blind, randomized, sham-controlled, cross-over trial in older Veterans with MCI. Another significant strength of our study is the use of sham-coil treatment. Other researchers have tilted the coil by 90^0 to develop the sham-effect. However, this approach could still induce some voltage to the brain (Lisanby et al., 2001). In this study a commercially available sham coil was used to control for the look and sound of active stimulation. We have used sham coils successfully to blind subjects and raters in earlier protocols; however, we did not attempt to control for the feel of rTMS using electrical stimulation of the scalp as in previous studies (Mennemeier et al., 2009). Other strengths include the high adherence rate and use of blinded raters. Thus, rTMS is a potential option for treatment of apathy in MCI with a potential to rapidly improve apathy and to reduce decline in cognition. Future studies need to include robust batteries of cognition to delineate the effects of rTMS on cognition. If replicated in larger studies, this finding could have significant impact on the trajectory of neurodegeneration. Studies of longer treatment duration and follow-up are needed, to study if such a treatment alters the dementia conversion rates among those with MCI. Future studies also need to include frequent measure of outcome measures to find the earliest response, and determine the dose response with rTMS.

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Highlights

- 10 Hz rTMS treatment is feasible in patients with comorbid MCI and apathy.
- Apathy and cognition improved significantly with the active treatment compared to the sham treatment.
- No participant dropped out of the study due to adverse events.
- Adverse events were transient and did not differ between active or sham treatment.

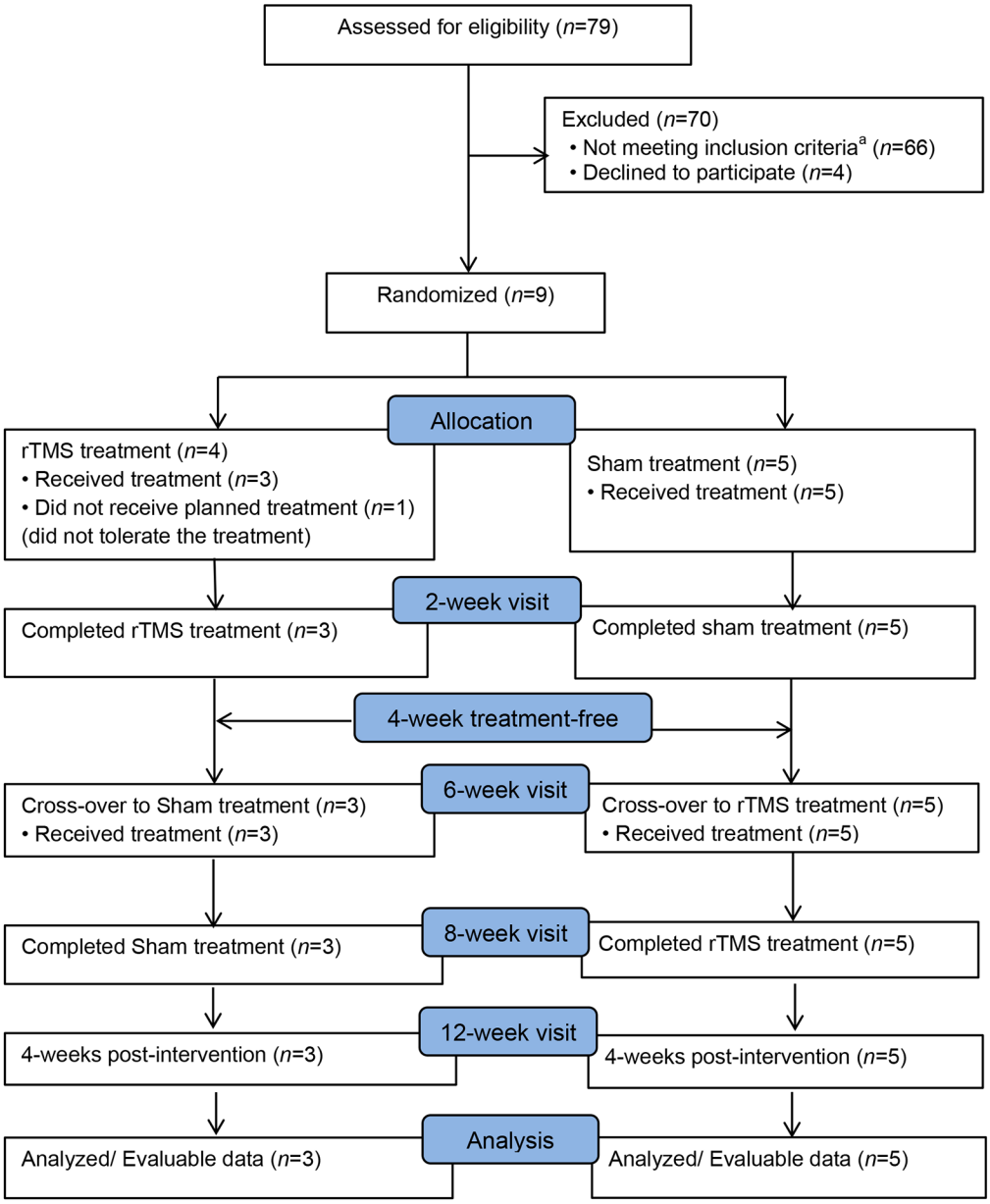

Figure 1:

Screening, Enrollment and Participation

[a] Reason for exclusion: 8-substance abuse, 8-travel, 5-time, 5-bipolar disorder, 5-recent start of antidepressants, 2-did not meet criteria for MCI, 4-brain injuries, 7-contraindicated medication (bupropion), 4-implants, 1- seizure disorder, 1-another study, 7-younger age, 9-unknown.

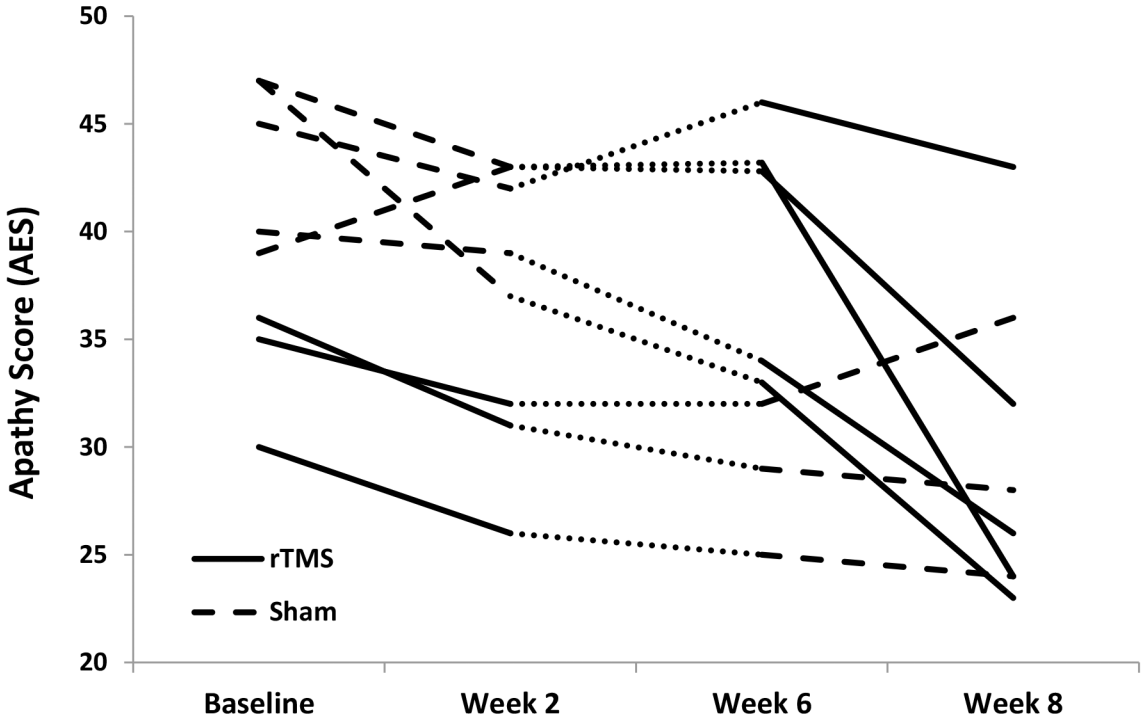

Figure 2:
Apathy Evaluation Scores over time

Table 1:

Descriptive characteristics according to the randomized groups

	All subjects (*N*=9)	rTMS-Sham (*N*=4)	Sham-rTMS (*N*=5)	*Statistic*	*p*-value[a]
Continuous variables	**mean (SD)**	**mean (SD)**	**mean (SD)**		
Age in years	65.6 (9.3)	68.0 (10.0)	64.0 (9.0)	t_7=0.61	0.562
Anthropometry					
Height (inches)	70.2 (3.1)	71.0 (2.2)	69.5 (68.5)	t_7=0.70	0.508
Weight (lbs.), median (IQR)	181.4 (175.5–189.4)	178.5 (158.2–183.1)	189.4 (177.5–231.0)	Z=−1.10	0.270
BMI (kg/m^2)	27.6 (5.8)	23.9 (3.6)	30.6 (5.7)	t_7=−2.05	0.079
Categorical variables	***n* (%)**	***n* (%)**	***n* (%)**		
Male	8 (89%)	4 (100)	4 (80)	FET	>0.999
Race				FET	>0.999
Non-Hispanic Caucasian	4 (44)	2 (50)	2 (40)		
Non-Hispanic African-American	5 (56)	2 (50)	3 (60)		
Education Category				X^2_2=3.99	0.167
High School diploma	7 (78)	2 (50)	5 (100)		
Bachelor's degree	1 (11)	1 (25)	0 (0)		
Professional/Graduate degree	1 (11)	1 (25)	0 (0)		
Concomitant medications					
Anti-Depressants	4 (44)	1 (25)	3 (60)	FET	0.524
Acetylcholinesterase Inhibitors	0 (0)	0 (0)	0 (0)	FET	>0.999
Memantine	0 (0)	0 (0)	0 (0)	FET	>0.999
Comorbidities					
Hypertension	5 (56)	2 (50)	3 (60)	FET	>0.999
Diabetes	3 (33)	1 (25)	2 (40)	FET	>0.999
Depression	5 (56)	2 (50)	3 (60)	FET	>0.999
Coronary Artery Disease	2 (22)	0 (0)	2 (40)	FET	0.444
Hypothyroidism	2 (22)	2 (50)	0 (0)	FET	0.167
Hyperlipidemia	5 (56)	2 (50)	3 (60)	FET	>0.999
Degenerative Joint Disease	5 (56)	2 (50)	3 (60)	FET	>0.999
Hearing Loss	5 (56)	3 (60)	2 (40)	FET	0.524
Mild Cognitive Impairment	9 (100)	4 (100)	5 (100)	FET	>0.999

[a] *p*-values calculated using the two-sample *t*-test, nonparametric Mann-Whitney test (normal approximation, Z), or Fisher's exact test (FET) or exact chi-square test (education category).

IQR: Interquartile range

Table 2:

Baseline measures according to the randomized groups

	All subjects (*N*=9) mean (SD)	rTMS-Sham (*N*=4) mean (SD)	Sham-rTMS (*N*=5) mean (SD)	*t*	*p*-value[a]
Primary end point					
Apathy Evaluation Scale	39.7 (4.4)	35.8 (4.9)	43.6 (3.8)	t_7=−2.70	0.031*
Secondary end points					
Modified Mini Mental State Exam	90.8 (3.8)	93.3 (3.4)	88.2 (4.2)	t_7=1.94	0.094
Mini Mental State Exam	25.6 (2.1)	27.3 (1.7)	24.2 (2.4)	t_7=2.14	0.070
Trails Making Test A	52.1 (12.3)	53.8 (13.3)	50.8 (12.9)	t_7=0.34	0.747
Trails Making Test B	142.6 (30.1)	150.3 (34.8)	136.4 (28.2)	t_7=0.66	0.529
Executive Function - 25 (Exit-25)	10.3 (4.1)	8.8 (4.3)	11.6 (4.4)	t_7=−1.03	0.335
Activities of Daily Living	23.6 (0.6)	24.0 (0.0)	23.2 (1.1)	-	Non-Est[b]
Instrumental Activities of Daily Living	20.5 (3.1)	20.8 (2.6)	20.2 (3.6)	t_7=0.26	0.805
Cognitive Global Impression - Severity	4.3 (0.5)	4.0 (0.0)	4.6 (0.5)	t_4=−2.45	0.071
Zarit Burden Scale	17.8 (10.7)	18.0 (11.3)	17.7 (12.6)	t_4=0.03	0.974

[a] *p*-values calculated using the two-sample *t*-test; unequal variance t-test was used for CGI-severity.

[b] Non-Estimable due to ceiling effect (i.e., only 2 subjects had less than perfect score)

* *p* value significant at < 0.05

Table 3:

Changes from baseline in outcomes with rTMS and sham treatments and the differences between the two treatments

Variables	Change with rTMS treatment (*n*=8) Mean (95% CI)	Change with Sham treatment (*n*=8) Mean (95% CI)	Difference[a] Mean (95% CI)	*t*	*p*-value[b]
	Primary end point				
AES	−7.4 (−11.9 to −2.8)	−1.5 (−6.1 to 3.1)	−5.9 (−11.6 to −0.2)	t_5=−2.66	0.045*
	Secondary end points				
3MS	5.0 (2.2 to 7.8)	−0.2 (−3.1 to 2.7)	5.2 (1.2 to 9.2)	t_5=3.34	0.021*
MMSE	2.9 (1.6 to 4.2)	−0.6 (−2.0 to 0.8)	3.4 (1.9 to 5.0)	t_5=5.75	0.002*
TMT-A	−3.1 (−13.2 to 7.0)	1.5 (−8.7 to 11.6)	−4.6 (−8.8 to −0.3)	t_5=−2.74	0.041*
TMT-B	−15.3 (−55.2 to 23.6)	−24.2 (−63.6 to 15.1)	8.4 (−47.5 to 64.3)	t_5=0.39	0.715
TMT-B errors	−0.9 (−4.1 to 2.3)	−1.7 (−4.9 to 1.5)	0.8 (−2.3 to 3.9)	t_5=0.66	0.539
Exit-25	−2.8 (−6.1 to 0.5)	−1.2 (−4.8 to 2.4)	−1.6 (−6.2 to 3.0)	t_5=−0.89	0.413
IADL	0.6 (−0.3 to 1.5)	0.8 (−0.2 to 1.7)	−0.1 (−1.2 to 0.9)	t_5=−0.32	0.761
CGI-S	−1.3 (−2.1 to −0.6)	−0.6 (−1.4 to 0.2)	−0.7 (−1.7 to 0.3)	t_5=−1.72	0.146
CGI-I	−0.7 (−1.6 to 0.2)	1.8 (0.9 to 2.8)	−2.5 (−3.8 to −1.1)	t_5=−4.76	0.005*
ZBS	0.5 (−27.7 to 28.8)	−2.1 (−37.4 to 33.1)	2.7 (−34.2 to 39.5)	t_1=0.92	0.526

[a]All means are estimates from a repeated measures model of 2-week change from baseline. Difference reflects rTMS group change minus sham group change and is adjusted for corresponding baseline measure, crossover sequence, and week.

[b]*p*-values comparing rTMS and sham treatment are model-based.

AES – Apathy Evaluation Scale; ADL – Activities of Daily Living; IADL – Instrumental Activities of Daily Living; 3MS – Modified Mini-Mental State Exam; MMSE – Mini Mental State Exam; TMT-A – Trails Making Test A; TMT-B – Trails Making Test B; TMT-B errors – Trails Making Test B errors; Exit-25 – Executive function-25; CGI-I – Clinical Global Impression-Improvement; CGI-S – Clinical Global Impression-Severity; ZBS – Zarit Burden Scale

*p value significant at < 0.05