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Repetitive transcranial magnetic stimulation for apathy in mild cognitive impairment: A double-blind, randomized, sham-controlled, cross-over pilot study

Prasad R. Padala[a,b,c,*], Kalpana P. Padala[a,c], Shelly Y. Lensing[a,d], Andrea N. Jackson[a], Cassandra R. Hunter[a], Christopher M. Parkes[a], Richard A. Dennis[a,c], Melinda M. Bopp[a], Ricardo Caceda[e], Mark S. Mennemeier[f], Paula K. Roberson[a,d], Dennis H. Sullivan[a,c]

[a] Geriatric Research Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, AR, USA
[b] Department of Psychiatry, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[c] Department of Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[d] Department of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[e] Department of Psychiatry, Stony Brook University Medical Center, Stony Brook, NY, USA
[f] Neurobiology and Developmental Sciences, University of Arkansas for Medical Sciences, Little Rock, AR, USA

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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 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.

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% to 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

* Correspondence to: 2200 Fort Roots Drive (3J/NLR), North Little Rock, AR 72114, USA.
E-mail address: Prasad.Padala@va.gov (P.R. Padala).

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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., 2005; Zhang et al., 2015). Modest improvements in apathy and cognitive correlates have been noted with dopaminergic agents such as methylphenidate (Padala et al., in press; 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., in press). 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 33 dB (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 10 Hz, 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 min including time for set up and 37.5 min 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)