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Combining therapeutic approaches: rTMS and aerobic exercise in post-stroke depression: a case series

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Abstract

Objective and importance—Residual effects of stroke include well-documented functional limitations and high prevalence of depression. Repetitive transcranial magnetic stimulation (rTMS) and aerobic exercise (AEx) are established techniques that improve depressive symptoms, but a combination of the two has yet to be reported. The purpose of this case series is to examine the safety, feasibility, and impact of combined rTMS and AEx on post-stroke depression and functional mobility.

Clinical presentation—Three participants with a history of stroke and at least mild depressive symptoms (Patient Health Questionnaire-9 = 5).

Intervention—Both rTMS and AEx were completed 3 times/week for 8-weeks. rTMS was applied to the left dorsolateral prefrontal cortex, 5000 pulses/session at 10 Hz, at an intensity of 120% of resting motor threshold. AEx consisted of 40 min of treadmill walking at 50–70% of heart rate reserve.

Results—Depressive symptoms improved in all three participants, with all demonstrating response (≥ 50% improvement in symptoms) and likely remission. All participants improved their Six Minute Walk Test distance and Participants 1 and 2 also improved Berg Balance Scale scores. Participants 1 and 3 improved overground walking speeds. No serious adverse events occurred.

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with the application of rTMS or AEx and the participants' subjective reports indicated positive responses. Adherence rate for both rTMS and AEx was 98%.

Conclusion—Combined treatment of rTMS and AEx appears safe, feasible, and tolerable in individuals with a history of stroke and at least mild depressive symptoms. All participants had good compliance and demonstrated improvements in both depressive symptoms and walking capacity.

Keywords

Stroke; depression; post-stroke depression; repetitive transcranial magnetic stimulation (rTMS); aerobic exercise; rehabilitation

Introduction

Each year in the United States an estimated 795,000 individuals experience a stroke.¹ Since the death rate from acute stroke has declined in conjunction with medical care advancements, stroke is now the leading cause of long-term disability.¹ Post-stroke rehabilitation focuses largely on treating the residual physical and cognitive impairments but the neuropsychiatric sequelae are often underappreciated.

Depression is the most common post-stroke neuropsychiatric disorder,² affecting an estimated 29–33% of stroke survivors.^{3,4} Consequently, at any given time nearly 2 million individuals in the United States are dealing with post-stroke depression (PSD). Studies have demonstrated that PSD can significantly compromise recovery⁵ and quality of life³ and increase mortality risk.⁶

Individual response to antidepressant medications for the treatment of depression is variable. Patients are often treated with multiple medications at different dosages before identifying an effective prescription. This process can take months, and even then, medications are not effective for about 30% of depressed patients.⁷ The response rate (50% decrease in depressive symptoms) in individuals with major depressive disorders (MDD) is only 46% and remission (no depressive symptoms) is achieved in only 28–33% of those with MDD after the first medication trial after depression diagnosis.⁸ Approximately, one-third of those who experience remission will relapse into another depressive episode within the next year.⁸

Treatment of depression following stroke has additional challenges. A recent Cochrane review found that pharmacological treatment for PSD yields a small but significant effect.⁹ More importantly, however, a significant increase in adverse events was also found.⁹ Challenges with pharmacological treatment of PSD include difficulty of pinpointing the correct medication and dosage, limited benefits on depressive symptoms, increased adverse events, and increased risk of polypharmacy; thus alternative approaches for effective PSD treatment are needed.

Daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) is a food and drug administration (FDA) approved treatment for depression that has been shown to be safe and effective with minimal side effects.¹⁰ Despite the benefits of rTMS, its investigation in individuals post-stroke is limited.^{11–13} Initial studies indicate that high frequency rTMS

improves symptoms of PSD, but these studies used a smaller rTMS dose, whether number of pulses and/or intensity, than used in the FDA trial.^{10,12,13} Some studies suggest that rTMS efficacy has a dose-response effect.^{14,15} Therefore, PSD trials using the FDA approved dosage are needed in order to assess safety while possibly maximizing the benefit of rTMS for PSD.

Aerobic exercise (AEx) has a dose-dependent benefit on depression in the neurologically healthy population.^{16–19} Compared to a control condition, exercise has a moderate effect on decreasing depressive symptoms.²⁰ When compared to psychological or pharmacological therapies, exercise appears to be equally effective²⁰ and is a recommended adjunctive treatment with antidepressants.²¹ Eng and Reime found this also holds true for the subacute and chronic stroke population as they reported that structured higher intensity exercise programs could possibly prevent and reduce post-stroke depressive symptoms.²² Additional benefits of AEx post-stroke, such as treadmill walking, include improvements in both cardiorespiratory fitness and functional mobility.²³

As shown in previous studies, rTMS and AEx are effective at treating depression. Independently both are attractive options as treatment adjuvants. In addition to improving depressive symptoms, treadmill walking has the added benefit of being an established locomotor rehabilitation approach. To date, the potential for combining these treatment approaches has not been reported. Thus, the purpose of this case series is to assess the safety, feasibility, and impact of combined rTMS and AEx on depressive symptoms, walking capacity, balance, and gait speed in individuals post-stroke.

Case description

This study was approved by the Institutional Review Board at the Medical University of South Carolina as part of a larger, on-going trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03056287) Identifier: NCT03056287). Prior to participation, written informed consent was obtained from each participant.

Three individuals post-stroke with depressive symptoms enrolled in this case series. Inclusion criteria were: (1) age 50–85; (2) mild to severe depressive symptoms upon enrollment (Patient Health Questionnaire-9 (PHQ-9) ≥ 5); (3) prior history of stroke with residual paresis in the lower extremity (Fugl-Meyer Assessment of Lower Extremity Motor (FMA-LEM) score <34); (4) not taking antidepressant medication or able to continue the currently prescribed dose throughout the study; (5) provision of informed consent. Exclusion criteria included: (1) unable to ambulate at least 150 feet prior to stroke or experienced intermittent claudication while walking; (2) history of congestive heart failure, unstable cardiac arrhythmias, hypertrophic cardiomyopathy, severe aortic stenosis, or angina or dyspnea at rest or during ADLs; (3) history of COPD or oxygen dependence; (4) pre-existing neurological disorders, dementia, or previous stroke; (5) history of major head trauma; (6) legal blindness or severe visual impairment; (7) life expectancy <1 year; (8) severe arthritis or other problems that limit passive ROM; (9) history of deep vein thrombosis or pulmonary embolism within 6 months; (10) uncontrolled diabetes with recent weight loss, diabetic coma, or frequent insulin reactions; (11) severe hypertension with

systolic >200 mm Hg and diastolic >110 mm Hg at rest; (12) attempt of suicide in the last 2 years; (13) current enrollment in a clinical trial to enhance motor recovery; (14) currently exercising 2 times per week (20 min); (15) presence of non-MR compatible implants, pregnancy, or severe claustrophobia; (16) history of seizures or taking medications that could increase risk for seizures. All participants completed a graded exercise tolerance test and were approved for participation by the study cardiologist. Participants were provided remuneration for each study visit attended.

Outcome measures

Outcomes were assessed pre- and post-intervention for all participants.

Depressive symptoms

The PHQ-9 was used to assess depressive symptoms.^{24,25} This tool is widely accepted for assessing depressive symptoms and has been found to be reliable and valid in various clinical settings and multiple populations, including post-stroke.^{26–28} The PHQ-9 questions how frequently each of the nine specific depressive symptoms described by *American Psychiatric Association's Diagnostic and Statistical Manual* (DSM-IV) have been experienced over the past 14 days: 0-none at all, 1-several days, 2-more than half the days, 3-nearly everyday. The total score (0–27) indicates the degree of depressive symptoms: 0–4 none; 5–9 mild; 10–14 moderate; 15–19 moderately severe; 20 severe. A total score of 10 has been cited as the cut-off for probable major depressive disorder (MDD).²⁹ In individuals post-stroke, a total score of 10 has 91–100% sensitivity and 86–89% specificity for MDD.^{26,28}

Walking capacity

Walking capacity was assessed with the Six-Minute Walk Test (6MWT). Participants walked as far as possible for 6 min on a standardized hallway without seated rest. They were permitted to use their orthotic and/or assistive devices, but study staff did not provide physical assistance. This test has been found to be reliable and valid in individuals post-stroke³⁰ and is a commonly used measure in research and in the clinic.

Balance

The Berg Balance Scale (BBS) consists of 14 different static and dynamic activities, ranging from static sitting to standing on a single leg.³¹ Each task is scored between 0 (requires some degree of assistance) to 4 (complete independently) and the sum of 14 activities equals the total score with a maximum of 56. The BBS has been found to be reliable and valid in individuals post-stroke^{31–33} and a score of <45/56 is indicative of a balance impairment.^{34,35}

Gait speed

The GAITRite® WalkWay System (CIR Systems Inc., Franklin, NJ) was used to measure overground gait speed. Participants wore a safety harness attached to an overhead track to prevent falls without offering bodyweight support. No assistive devices were used when ambulating over the GAITRite®, but the use of an orthotic was permitted. The GAITRite® WalkWay was 14 feet long and the participants walked an additional 5 feet at both the

beginning and end of the WalkWay to account for acceleration and deceleration. Each participant walked three times at both self-selected (SSWS) and fastest comfortable (FCWS) walking speeds and the average of the three trials was taken. Speed was recorded in meters/second (m/s).

Participants

See Table 1.

Participant 1 was a 64-year-old, married, African-American man who was 65 months post right-hemispheric ischemic stroke. His baseline depression scores (PHQ-9 = 11) indicated probable MDD and his baseline FMA-LEM was 25. Participant 1 ambulated in the community with a single point cane (SPC) without an orthotic and drove himself 8.5 miles (about 20 min) to each visit. Pre-intervention SSWS was 0.87 m/s and FCWS was 1.48 m/s.

Participant 2 was a 58-year-old, married, African-American woman who was 34 months post left-hemispheric hemorrhagic stroke and had an initial PHQ-9 score of 6. Her baseline depression score indicated mild depressive symptoms. She ambulated in the community using a custom hinged ankle foot orthotic and a SPC. Participant 2's husband drove her about 1 h (46 miles) to each visit. Her initial FMA-LEM was 20. Pre-intervention SSWS was 0.28 m/s and FCWS was 0.33 m/s.

Participant 3 was an 82-year-old, married, Caucasian man who was 3 months post right-hemispheric ischemic stroke. His initial PHQ-9 score of 11 also indicated probable MDD and his baseline FMA-LEM score was 30. Within the community, he ambulated without an assistive device or orthotic and his wife drove him 9.2 miles (about 20 min) to each visit. Baseline SSWS was 0.66 m/s and FCWS was 0.98 m/s.

Interventions

Participants were seen 3 times/week for 8 weeks for a total of 24 sessions. Each session consisted of two parts: AEx and rTMS. The specific intervention (AEx or rTMS) administered at the beginning of each session was alternated weekly (e.g. Week 1: rTMS then AEx, Week 2: AEx then rTMS) to account for any possible order effects.

rTMS

rTMS is a non-invasive brain stimulation therapy.³⁶ During application, an electromagnetic coil is placed on the participant's head.³⁶ The coil generates a magnetic field and when pulsed the field induces an electrical current in the brain.³⁶ When placed on the motor cortex, a contraction of the muscle(s) in the anatomical region controlled by the area stimulated can be observed.³⁶ When using rTMS to treat depression, the coil is placed in the area of the left dorsolateral prefrontal cortex and a rapid succession of pulses is used.³⁶

The Neurostar TMS Therapy[®] System (Neuronetics Inc., Malvern, PA) delivered rTMS using the specific FDA approved protocol for participant positioning and determination of the motor threshold.³⁷ During the first session, the resting motor threshold (RMT), the minimum stimulation intensity of a single pulse required to obtain a visible contraction, of

the right abductor pollicis brevis was found using the automatic Neurostar RMT Assist algorithm.³⁷ The coil was then moved anteriorly 5 cm from the RMT site for the rTMS application to the left dorsolateral prefrontal cortex.^{10,38} Positional settings were recorded and used to ensure reproducible coil placement between sessions.

The FDA approved rTMS treatment protocol for depression, 3000 pulses/session at 10 Hz (4 s on and 26 s off) for a total of 75 stimulation cycles at 120% of RMT, 5 times/week,^{10,37} was modified to match the weekly frequency of AEx of 3 times/week. The weekly dosage (number of pulses $\times$ percentage of RMT) was kept consistent between the FDA protocol and our protocol. The specific protocol used for this study required 5000 pulses/session at 10 Hz (5 s on and 10 s off) for a total of 100 stimulation cycles, with an intensity of 120% of the RMT, 3 days/week for 8 weeks. To ensure tolerability, an individualized dosage increase was utilized with the goal of achieving the full dose by Week 2.

Aerobic exercise

A modified version of the post-stroke protocol for aerobic training by Macko et al. was used.³⁹ Based on data from the graded exercise tolerance test, heart rate reserve (HRR) was determined. Training began during Week 1 at an average intensity of 50–55% of HRR and progressed by ~5% every two weeks to achieve 65–70% of HRR by Weeks 7 and 8. To attain the target heart rate (HR), study staff adjusted treadmill speed and/or incline as appropriate. HR was monitored continuously, while blood pressure (BP) was taken prior to each session, every 5–10 min during a session, and after each session. Training was not initiated or was stopped if systolic BP was >200 mm Hg and diastolic >110 mm Hg or if an abnormal response to exercise was noted. To control for medications that could impact cardiovascular response to AEx, all participants reported their rate of perceived exertion (RPE) every 5 min using the 15-point Borg RPE scale.⁴⁰ Intensity of AEx was decreased if RPE ≥ 18 .

The type of training for each session, steady state or interval, was alternated daily. Interval training was performed using a 1:1 work to rest ratio with interval speeds exceeding steady state speeds. Intervals were 2 min in duration during Weeks 1–3, 3 min during Weeks 4–6, and 4 min during Weeks 7–8. The goal was for participants to walk continuously for 40 min, with rest breaks permitted as needed. To ensure compliance, participants were permitted to ambulate 20 to 40 min during Week 1, but were encouraged to complete 40 min during Weeks 2–8.

All participants wore a Polar (Polar Electro, Lake Success, NY) heart rate monitor for continuous HR monitoring as well as a safety harness connected to an overhead track to ensure safety without offering bodyweight support. All training was completed on either a Woodway (Woodway World USA Inc., Waukesha, WI) or SCIFIT (SCIFIT Inc, Tulsa, OK) treadmill with supervision of 1 to 2 study personnel. Participants were permitted to use their orthotic device as well as the treadmill handrails during training.

Outcomes

Interventions

rTMS—The modified rTMS treatment protocol was completed without serious adverse events. Participants reported scalp discomfort at the stimulation site (Participants 1–3) as well as occasional headaches following treatment sessions (Participants 1 and 3). The reported stimulation site discomfort decreased after a few sessions from 9/10 to 2/10 at a maximum. Participant 2 reported feeling “fuzzy” after Treatment Day 7, but this symptom resolved. rTMS treatment was initiated at 80% of RMT for Treatment Day 1 for all participants and the full dosage was achieved by Week 2, Treatment Day 6 at the latest. See Figure 1 for illustration of dosage application for Treatment Days 1–10. Participant 1 completed 23 rTMS sessions while Participants 2 and 3 completed all 24 sessions.

Aerobic exercise—Participants completed the AEx protocol without any serious adverse events. Some reports of fatigue (Participant 3) and muscle cramping/spasms (Participants 1) were noted but did not interfere with training. All participants achieved walking for 40 min by Week 2, Treatment Day 5. Participants 1 and 3 completed all 24 AEx sessions, while Participant 2 completed 23 sessions.

Outcome measures—See Table 2 for participant specific pre- and post-intervention data.

Depressive symptoms—PHQ-9 scores (Figure 2(a)) for all three participants decreased to the level where none would be described as having depressive symptoms (PHQ-9 score of 0–4). Based on standard definitions, all participants demonstrated a clinical response (at least 50% improvement in symptoms). Participants 1 and 3, who had probable MDD pre-intervention, also achieved likely remission of depressive symptoms.

Walking capacity—All participants increased their 6MWT distance (Figure 2(b)) post-intervention. Participants 1 and 3 exceeded the minimal clinically important difference (MCID) of 34.4 meters.⁴¹ Participant 2 was only 9.40 meters short of meeting the MCID.

Balance—Two of the three participants improved their BBS scores (Figure 2(c)). Participants 1 and 2 had a positive improvement and both met the MCID for the BBS post-stroke of 4.13 points.³² Participant 3 demonstrated a two-point decrease in his score of 54/56 to 52/56. A decreased score on this outcome is not expected but post-training values are still well above threshold for fall risk, given the high baseline score. Pre- and post-intervention, Participants 1 and 3 did not demonstrate balance impairments (score <45/56).³⁴ Based on BBS scores, Participant 2 had a balance impairment pre-intervention and no balance impairment post-intervention.

Walking speed—Participants 1 and 3 improved both SSWS and FCWS, while Participant 2 demonstrated a slight decrease at both speeds (Figure 2(d)). When assessing individual changes and their relationship to function, Participant 1 progressed from being classified as a community ambulator to being able to cross streets and approaching normal walking speed.⁴² Participant 2 remained a household ambulator at the end of the intervention, but

Participant 3 progressed from a limited community ambulator to a community ambulator.⁴² Participants 1 and 3 both exceeded the MCID for walking speed.⁴³

Subjective reports—Participant 1: During Treatment Day 17, this participant reported that other people are telling him he is smiling more and “I do not let things bother me like I used to.” On Treatment Day 18, he also reported, “This really seems to be working. I am really laughing and smiling more.” On Treatment Day 22, he reported feeling more motivated and talkative and at the end of Treatment Day 24, he reported that his stress levels had decreased and he is able to handle stressful situations better.

Participant 2: During Treatment Day 10, she reported that she is walking around her home more without her cane since she is feeling more stable.

Participant 3: During post-intervention assessments he reported that there is a change in his stamina and “I can now work up to two and a half hours straight in the yard without help and up to three hours with help.” This is compared to 1–1.5 h prior to intervention. He also stated, “I have less fear of losing my balance when I walk fast.”

Discussion

The findings from this case series indicate that exercise and rTMS can be safely combined in individuals post-stroke with depressive symptoms without overwhelming them with additional commitments or procedures. Specifically, applying a modified FDA approved rTMS protocol of 5000 pulses/session at 10 Hz at 120% the RMT, 3 days/week for 8 weeks, combined with 40 min of AEx was feasible, tolerable, and had positive results on post-stroke depressive symptoms and walking capacity among these three participants. No participants withdrew from the study and no serious adverse event occurred. Adherence rate for both rTMS and AEx was 98%. Reports of scalp discomfort at stimulation site and headaches with rTMS and fatigue and muscle cramps/spams with AEx are known and expected complaints for both interventions.

To our knowledge, this is the first publication of rTMS combined with AEx to treat depressive symptoms in individuals post-stroke. Combining rTMS and AEx had a positive subjective and objective impact on the participants. The greatest improvements in depressive symptoms, walking capacity, and walking speeds occurred in Participants 1 and 3, both of whom had probable MDD prior to treatment. These results indicate that within our three participants, remission of post-stroke depressive symptoms accompanied improvements in mobility. In a longitudinal study of community-dwelling depressed older adults, the remission of depression was associated with improved functional mobility,⁴⁴ so it is possible this could hold true for individuals with PSD. Prefrontal rTMS may also improve an individual's resilience and desire to exercise more frequently and possibly at a greater intensity. A prefrontal rTMS study in healthy young adults showed they had increased resilience after even a single session.⁴⁵

Despite these results, no direct causality regarding the positive results of this study can be inferred. Changes in depressive symptoms and outcomes could be the result of 8-weeks of social interaction with study staff or an increase in community engagement, instead of

directly due to the interventions. This case series did not demonstrate a greater benefit of combining rTMS and AEx compared to individual intervention(s). Investigating the potential superiority of combined interventions was not the intention as all participants received both rTMS and AEx. Additionally, the influence of cortical damage on individual responses was not explored given the scope of this case series. However, lesion size and/or location could be an important variable for stratification or a cofactor in analysis. It is important to acknowledge that this is a case series with only three participants post-stroke. Due to the small sample size and the heterogeneity of stroke and PSD, the external validity of this study is limited. A larger randomized control trial is needed to address the above limitations.

Even with these limitations, the findings of this case series indicate that combined rTMS and AEx treatment seems feasible in individuals with post-stroke depressive symptoms and appears to have an overall positive effect on outcomes. Further investigation with a controlled trial is justified to determine the impact of combined rTMS and/or AEx on depressive symptoms and functional mobility and to examine the relationship between remission of depression and functional mobility in individuals with PSD.

Conclusions

The outcomes of this case series suggest that combining rTMS and AEx is feasible and well-tolerated in individuals with at least mild depressive symptoms post-stroke. All participants had improved depressive symptoms and walking capacity, with varying improvements in balance and gait speeds. A larger controlled trial is needed to identify the possible relationships between changes in depressive symptoms and functional mobility post-stroke.

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Figure 1. Repetitive transcranial magnetic stimulation dose (number of pulses $\times$ percentage of resting motor threshold) for Treatment numbers 1 – 10. Treatment dose was maintained for all three participants for session 11–24.

Figure 2.

Pre- and post-intervention (Int.) scores for (a) Patient Health Questionnaire-9 (PHQ-9); (b) Six Minute Walk Test (6MWT); (c) Berg Balance Scale (BBS); (d) Gait speed both self-selected walking speed (SSWS) and fastest comfortable walking speed (FCWS).

Table 1

Participant characteristics.

	Gender	Race	Age ^a	Time since stroke ^b	FMA-LEM	Assistive device	Orthotic
Participant 1	M	AA	64	65	25	SPC	None
Participant 2	F	AA	58	34	20	SPC	Hinged AFO
Participant 3	M	C	82	3	30	None	None

Notes:

Abbreviations: M: Male; F: Female; AA: African-American; C: Caucasian; FMA-LEM: Fugl-Meyer Assessment-Lower Extremity Motor; SPC: Single Point Cane; AFO: Ankle Foot Orthotic.

^aYears.

^bMonths.

Table 2

Pre- and post-intervention data for each participant.

Participant	Pre-intervention					Post-intervention				
	PHQ-9	6MWT ^a	BBS	SSWS ^b	FCWS ^b	PHQ-9	6MWTa	BBS	SSWS ^b	FCWS ^b
Participant 11 ^c		272.50	46	0.87	1.48	2	331.6	51	1.06	1.83
Participant 6		95.70	37	0.28	0.34	3	120.70	47	0.26	0.25
Participant 11 ^c		393.80	54	0.66	0.98	4	449.28	52	1.29	1.49

Notes:

Abbreviations: PHQ-9: Patient Health Questionnaire-9; 6MWT: Six Minute Walk Test; BBS: Berg Balance Scale; SSWS: Self-Selected Walking Speed; FCWS: Fastest Comfortable Walking Speed.

^aMeters.

^bMeters/second.

^cProbable major depressive disorder (PHQ-9 10).