Effect of transcranial magnetic stimulation on postural control of individuals with major depressive disorder: A case report

Hamid Bateni[1] (ID)**, Elham Soltani[2], Kishwar Ali[3], Haiming Zhou[4] and Mujeeb U Shad[5,6,7]**

Abstract

Accidental falls and major depressive disorder (MDD) are two common conditions associated with aging. Initial treatment of MDD often starts with administering antidepressants, followed by transcranial magnetic stimulation (TMS) for treatment-resistant individuals. The purpose of this case study was to determine the effect of repetitive TMS (rTMS) on postural control of an individual with MDD. A 44-year-old male with recurrent severe MDD was assessed for postural balance during eyes closed and eyes open conditions, pre and post three consecutive sessions receiving high-frequency rTMS (NeuroStar). Total excursion and velocity of sway significantly decreased following rTMS treatment when eyes were closed ($p < 0.05$). Power of the sway changed, but the changes were not statistically significant. The fractal dimension confidence circle area decreased significantly in eyes closed trials ($p < 0.05$). It appears that rTMS application can potentially impact postural steadiness in individuals with MDD. Our results warrant further studies with larger study samples.

Keywords

Postural steadiness, major depressive disorder, transcranial magnetic stimulation

Introduction

Accidental falls and major depressive disorder (MDD) are two common conditions associated with aging.[1] Falls are the leading cause of death due to unintentional injuries.[2] Approximately 25% of older adults over the age of 65 fall once or more per year.[3] In addition, nearly 10% of older adults suffer from MDD,[4] which is a prevalent and debilitating psychiatric condition that influences all aspects of life. Patients with MDD have been shown to have neuronal atrophy and a loss of synaptic connections in the cortical and limbic brain regions.[5]

Studies have established a direct relationship between MDD and postural control deficits.[6] Initial treatment of MDD often starts with administering antidepressants. However, some antidepressants (e.g. fluoxetine, doxepin and amitriptyline) most likely debilitate psychomotor skills and postural control.[7,8] An alternative solution for treatment-resistant MDD is transcranial magnetic stimulation (TMS). During TMS sessions, non-invasive brain neuromodulation is achieved via a magnetic pulse (induced through a magnetic coil) that is delivered to the brain cortex, which in turn creates an inverted electric charge and depolarizes neurons in brain tissue.[9]

Recently, TMS has become a common modality to address symptoms of MDD when resistance to psychopharmacological treatments is experienced. Studies have shown that TMS treatment for MDD is highly effective.[10,11] The effect of TMS treatment on postural control, however, is not yet well understood. A recent study on stroke patients reported that TMS treatment may improve static postural stability and postural control, as determined by the Berg

[1]Physical Therapy Program, Northern Illinois University, DeKalb, IL, USA
[2]Psychiatry Program, The Valley Health System, Las Vegas, NV, USA
[3]General Psychiatry Services, Aurora, IL, USA
[4]Department of Statistics and Actuarial Science, Northern Illinois University, DeKalb, IL, USA
[5]The Valley Health System, Las Vegas, NV, USA
[6]University of Nevada Las Vegas, Las Vegas, NV, USA
[7]Touro University Nevada College of Osteopathic Medicine, Las Vegas, NV, USA

*Haiming Zhou is now affiliated to Daiichi Sankyo, Inc., Basking Ridge, NJ, USA

Corresponding Author:
Hamid Bateni, Physical Therapy Program, Northern Illinois University, 1425 W. Lincoln Hwy, DeKalb, IL 60115-2828, USA.
Email: hbateni@niu.edu

Balance Scale.[12] To our knowledge, no other studies have explored the potential effects of TMS treatment on the postural steadiness of individuals with MDD.

Hypothesis

Although the dorsolateral prefrontal cortex (DLPFC) is primarily associated with executive functions, its role in the control of posture, particularly during cognitively demanding and complex sensory tasks, is well established.[13–16] Cognitive impairments are shown to impact posture negatively by changing several variables of postural steadiness (e.g. sway velocity) and increasing the risk of accidental falls.[17,18] At the same time, cognitive disorders in different domains are highly prevalent in individuals with depressive disorders,[19–21] and often, symptoms of cognitive disorders persist even when symptoms of depression are in remission.[19] Considering this link between depression and poor postural balance,[22] a potential improvement of postural control may be anticipated when depressive symptoms are affected, particularly with treatment modalities that not only improve depressive but also cognitive symptoms as well. The standard high-frequency repetitive TMS (rTMS) protocol for individuals with depressive disorders is a non-invasive approach that aims to induce electrophysiological excitatory effects to improve DLPFC function by recruiting more neural resources and improving conflict resolution in cognitive control processing.[23] Thus, we anticipate that high-frequency rTMS, delivered under the standard protocol for MDD, may improve postural control via its antidepressant and precognitive effects as reflected by changes in postural sway variables. The purpose our case study is to identify whether high-frequency rTMS therapy can potentially affect postural steadiness as determined by time and frequency domain variables of postural sway.

Case report

Following approval of the Institutional Review Board at Northern Illinois University, a 44-year-old male with recurrent severe MDD (without psychotic features) and post-traumatic stress disorder was recruited to participate in this study in the summer of 2021. The participant scored 20 on the Patient Health Questionnaire-9 (PHQ-9)[24] and was taking bupropion HCL (150 mg), clonazepam (1 mg), prazosin HCL (5 mg), lamortrigine (200 mg), aripiprazole (15 mg), and benztropine (1 mg). Otherwise, the patient had no physical disability or visual or vestibular deficit that could potentially affect their balance, could ambulate without any assistance or use of an assistive device, and could stand upright independently for at least 10 min. The patient was not using any alcohol or recreational drugs, did not drink any caffeinated beverages at least 24 h prior to the tests and refrained from exercising heavily at least 8 h before the tests. The patient was scheduled for 36 rTMS sessions (one visit per day) and was tested before the first

session and then after visits 15, 16, and 17. The patient was required to sign a consent form prior to participation in the study. In addition, written informed consent was obtained from his representative to use the anonymous data for publication.

The participant received high-frequency rTMS (NeuroStar) over the left DLPFC using a figure-8 coil. The stimulus was set at 120% of the motor threshold and delivered at a frequency of 10 pulses per second. Each 30-s cycle consisted of 4 s of active stimulation with 26 s of no stimulation. A total of 3000 pulses was delivered per session. A Kistler force platform (Kistler Co., Winterthur, Switzerland) was used to collect position data for the center of pressure (COP) at 100 Hz. A LabVIEW program (National Instrument, Austin, Texas) was developed to collect postural sway data.

At each visit, the participant was randomly assigned to two standing conditions: (a) eyes open and (b) eyes closed before and after (pre-post) the rTMS application. The condition of eyes closed was included to estimate changes in postural steadiness when the visual information required for postural control was challenged. Considering that vestibular, visual, and sensory information are typically used to maintain upright posture, deterioration of any of these sources of information may reveal information regarding an individual's dependency on the lost source. These test conditions (i.e. eyes open, eyes closed) were repeated three times before and after treatment. Test orders (i.e. eyes open vs eyes closed) were block randomized (for pre and post treatment separately), with each condition presented once in each block.

During each session, the participant was instructed to stand straight and static with arms by their sides (bare feet, heels together, 5°–7° of toe-out) on the force platform. Data were collected for 45 s (Fs = 100). For the eyes closed condition, the participant was asked to close their eyes throughout the trial. While there were no specific resting periods implemented between trials, the participant was informed prior to and during the testing that they were welcome to request a rest time if needed. Anteroposterior and mediolateral time series data were filtered through a fourth-order zero phase Butterworth low-pass filter with a cutoff frequency of 5 Hz. The first 8 s and last 2 s of data were cut to remove any potential lead-in/lead-out effect. MATLAB and Toolbox Release 2012b (MathWorks, Inc., Natick, Massachusetts) were used to filter the postural sway data and to compute variables of interest. Time and frequency domain variables of postural sway were computed. A detailed explanation of the computation methods used for the variables and equations is available in the literature.[25–30] Total excursion of sway, identified as the total distance that the COP travels while standing in a static position, was computed by summation of the distance between two consecutive data points

$$total\ excursion\ of\ sway = \sum_{n=1}^{N-1} \sqrt{\frac{(AP[n+1]-AP[n])^2}{+(ML[n+1]-ML[n])^2}}$$
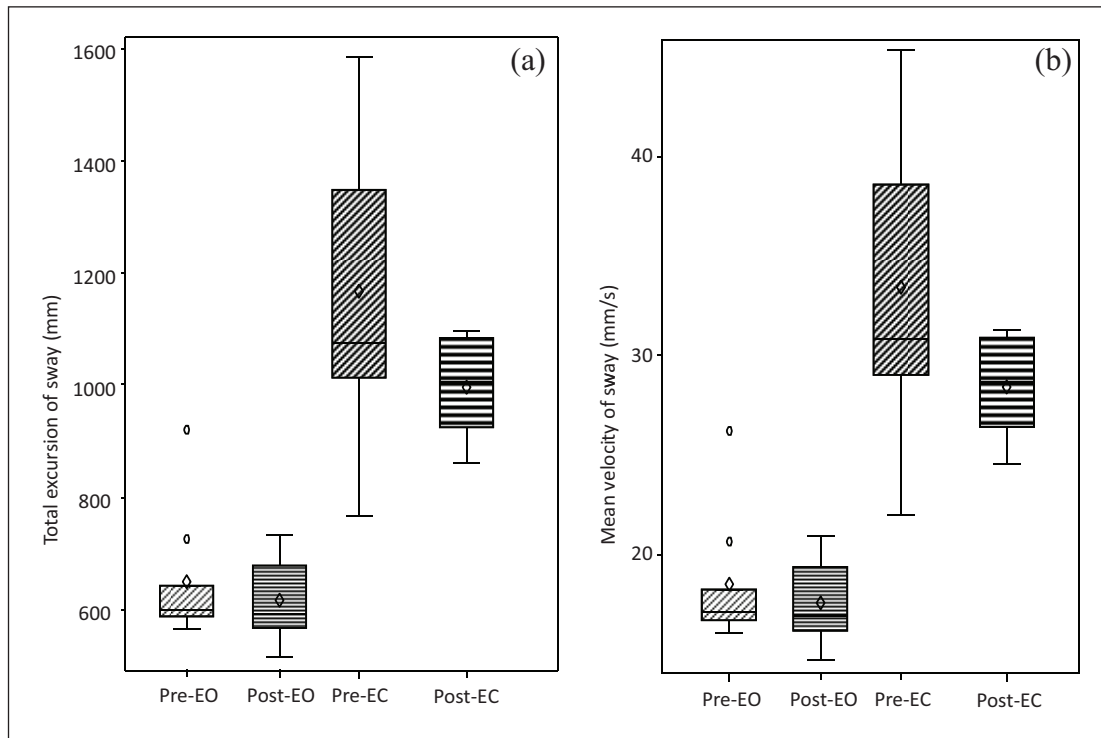
Figure 1. Figure depicts comparison of total excursion (a) and mean velocity (b) of sway pre and post TMS sessions. Two different conditions of eyes open (EO) and eyes closed (EC) are presented. Note the difference between eyes open and eyes closed conditions as well as constant changes following rTMS sessions.

Velocity of sway was calculated by dividing total excursion over time

$$Velocity\,of\,sway = \frac{total\,excursion\,of\,sway}{total\,time}$$

Power of sway signal was computed as the integrated area of the power spectrum, and 95% power frequency was determined as the point below which 95% of the total power was placed.[26]

Although we only tested one participant, the repeated measures allowed us to quantify the within-subject variation in the outcome measures. Therfore, it is reasonable to assume that the measures are independent after controlling for the four variables: Factor (i.e. pre and post), Condition (i.e. eyes open and eyes closed), Factor × Condition, and Visit. We first calculated means and standard deviations (SDs) on several outcome measures (including mean velocity, resultant power, and sway velocity) across the four possible groups created by Factor and Condition. Then, we used the general linear model (GLM) to model each outcome measure after controlling for Factor, Condition, Factor × Condition, and Visit. All statistical tests were 2-sided with a p value less than 0.05 indicating a statistically significant effect. All models were fit in SAS (version 9.4) using PROC GLM.

Following completion of the 36 rTMS sessions, the participant's PHQ-9 score was reduced from 20 (severe depression) on the first day of the treatment to 10 (mild depression).

Comparison of mean velocity (MVELO) of sway showed that the participant swayed at a lower velocity following rTMS treatment (18.5 ± 3.19 mm/s pre and 17.51 ± 2.1 mm/s post). When postural control was challenged by eliminating visual input (eyes closed), changes in velocity of sway following rTMS application were more substantial when the participant's eyes were closed as opposed to their eyes were open (33.38 ± 7.69 mm/s eyes closed—pre rTMS vs. 28.41 ± 2.45 mm/s eyes closed—post rTMS). Total excursion of postural sway also changed following rTMS application. The boxplots in Figure 1 also show the same pattern. After controlling for the visit effect, the GLM results (Table 1) show that no significant changes of mean velocity were observed pre and post rTMS for the eyes open condition, but mean velocity of sway was significantly reduced following rTMS sessions ($p = 0.005$). The R-square value indicates that the 83.7% within-subject variation was explained by Factor, Condition, and Visit. Figure 2 shows a trend that mean velocity of sway decreased over the three visits. At visit 3, the mean velocity was reduced to 14.37 (95% confidence interval (CI): 11.46–17.29) when the participant's eyes were open and 25.27 (95% CI: 22.35–28.19) when their eyes were closed.

The power of sway signal showed significant changes between the eyes open and eyes closed condition both before and after the rTMS sessions ($p < 0.05$). Comparison of sway signal power changes before and after rTMS sessions for

Table I. General linear model (GLM) results: estimates and standard errors (SEs) for certain effects.

Effect	MVELO (R-square = 0.837)			POWER_RD (R-square = 0.537)		
	Estimate	SE	p value	Estimate	SE	p value
Post-pre, eyes open	−0.983	1.650	.556	336.2	445.0	.456
Post-pre, eyes closed	−4.971	1.650	.005	848.5	445.0	.066
Post at visit = 3, eyes open	14.37	1.429	–	2386	385.4	–
Post at visit = 3, eyes closed	25.27	1.429	–	4344	385.4	–

MVELO: mean velocity; POWER_RD: resultant power.
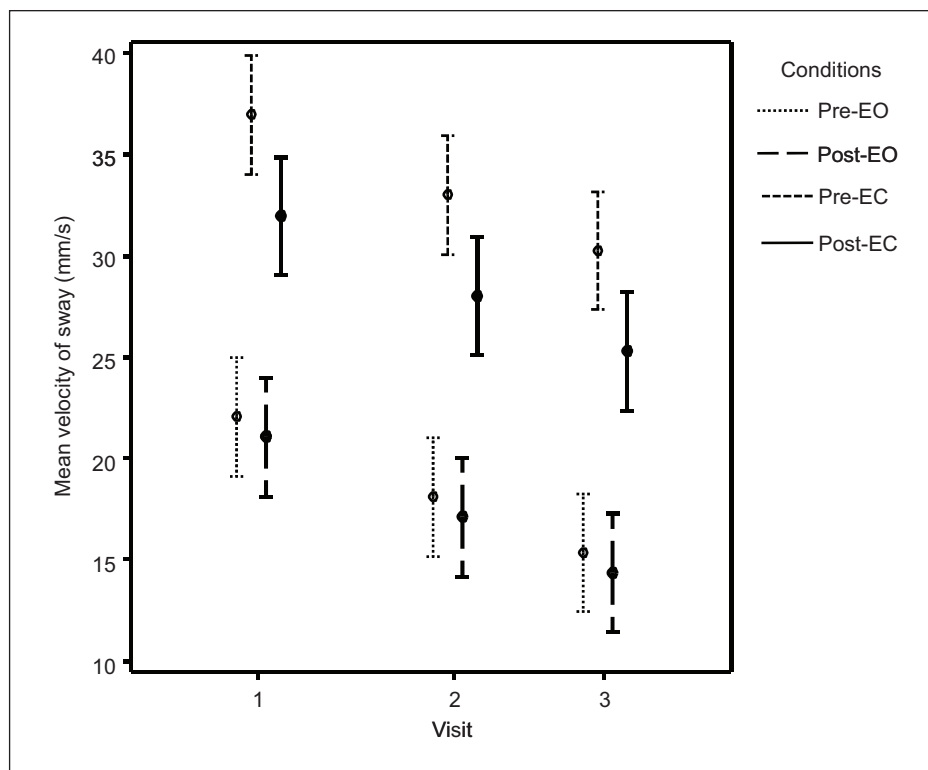
Figure 2. Figure illustrates fit for mean velocity of sway with 95% confidence limits and compares changes of postural velocity for different visits. Note significant and continued change of sway velocity following each visit.

each condition, however, did not show statistically significant changes (Figure 3).

The fractal dimension confidence circle area (FD_CC) was also compared between the two conditions and between pre and post rTMS sessions. Our results showed that FD_CC during the eyes open condition did not significantly change between pre and post rTMS session (p = 0.05). On the other hand, when eyes closed conditions were compared, the decrease of FD_CC following rTMS sessions was statistically significant (p < 0.05) (Figure 3).

Discussion

As expected, we noticed significant changes of postural sway between eyes open and eyes closed conditions.

Although changes of sway following rTMS sessions during eyes open trials occurred, these changes were not statistically significant. On the other hand, when postural control was challenged with the eyes closed condition, all postural sway variables were changed significantly. Total excursion of sway represents the total length of the COP path. An increase in total excursion of sway has previously been reported in the literature as a result of aging or lower extremity amputation.[31] Total excursion of COP, which is an indicator of poor postural stability, was substantially decreased in our patient following rTMS sessions. As expected, we noticed a similar pattern of changes in sway velocity before and after rTMS sessions. Improvement of time domain variables of postural sway, particularly sway velocity, indicates a decrease in the risk of falling. Velocity of sway is reported as
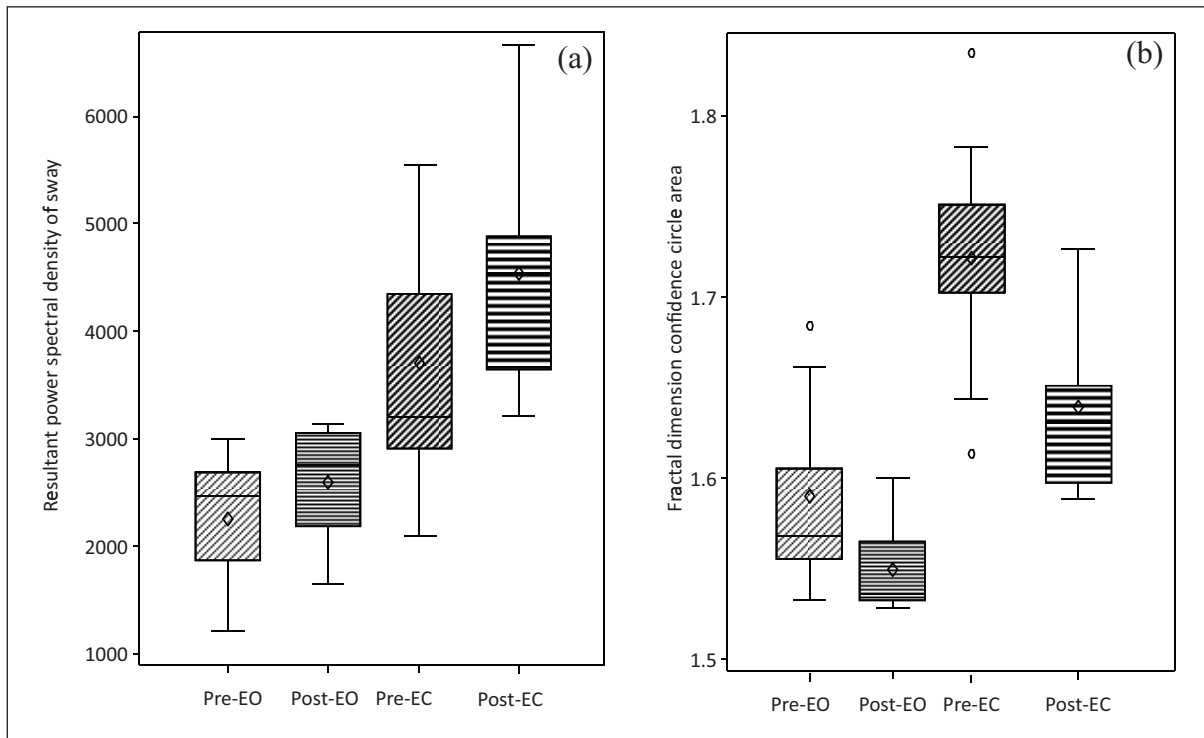
Figure 3. Figure presents the resultant power spectral density of sway (a) and fractal dimension confidence circle area (b) of sway signal. The figure shows pre and post TMS sessions as well as eyes open (EO) and eyes closed (EC) conditions. Note that changes between pre and post TMS sessions are always augmented when eyes are closed.

the main variable representing quality of postural control and the effect of aging.[26,32]

In our patient, we also assessed frequency domain variables of postural sway. Previous studies have suggested the use of frequency domain variables in conjunction with time domain variables (e.g. total excursion and sway velocity) to reveal more valuable information.[25,26,33] Analysis of the frequency content of a signal may reveal underlying changes that are often not observed in a time series.[34] Our results indicated significant changes in the power of sway signal following rTMS sessions. Although these changes were not substantial during eyes open trials, they were significantly higher in eyes closed trials following the rTMS sessions. Such changes may indicate increased simultaneous muscle activities that may not be well reflected in a time domain series.

We also compared fractal dimension of sway signal pre and post rTMS sessions. Fractal dimension of postural sway is a unitless measure indicating the degree to which a curve fills the space it encompasses.[26] It is suggested that a fractal dimension, when compared with other characteristics of sway, more accurately detects changes of postural sway.[35] We found that fractal dimension of postural sway substantially reduced following rTMS sessions. The increased pattern of changes in fractal dimension is consistent with those reported by Prieto et al.,[26] suggesting an increase of fractal dimension by aging. Therefore, rTMS treatment may have the potential to improve postural steadiness and reduce the risk of accidental falls.

Several limitations and confounders are associated with our findings. First, having a single subject prevents us from drawing general conclusions from our findings. The findings from this study are based on a single case and may be influenced by the patient's wakefulness level.[36] Our study participant complied with the instructions to refrain from caffeine or alcohol consumption at least 24 h before the test and heavy exercise at least 8 h before the test. However, other physical and physiological variables, such as stress level and hours of sleep the night before each testing session, were not controlled, and this may have affected the results. In addition, since our findings are based on a single case, placebo effects cannot be ruled out due to the lack of a sham rTMS condition. Another limitation of the study is that the study assessments were only conducted in the middle of the patient's 6-week rTMS course; future studies may have more significant findings when measuring postural control before the rTMS course and after the conclusion of 36 sessions of treatment. However, despite these limitations, our findings are interesting enough to warrant investigation in randomized controlled studies that can also examine the sustainability of rTMS-induced postural stability.

Conclusion

Overall, our results show substantial changes of time and frequency domain variables following high-frequency rTMS sessions over the left dorsolateral prefrontal cortex. Of note,

we show an improvement of postural sway after each individual rTMS session and an overall continuous reduction following three consecutive rTMS sessions. Our findings provide initial evidence for use of the high frequency left DLPFC rTMS protocol in improving postural control. This case report justifies further studies with larger sample sizes to determine the benefit of rTMS on improving postural control and reducing the risk of falls.

ORCID iD

Hamid Bateni 🔘 https://orcid.org/0000-0001-9083-1817

References

1. Liang Y, Rausch C, Laflamme L, et al. Prevalence, trend and contributing factors of geriatric syndromes among older Swedes: results from the Stockholm County Council Public Health Surveys. *BMC Geriatr* 2018; 18: 322.
2. National Center for Health Statistics. *Health, United States, 2016: with chartbook on long-term trends in health.* Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics, 2017.
3. Bergen G, Stevens MR and Burns ER. Falls and fall injuries among adults aged ⩾65 years—United States, 2014. *MMWR Morb Mortal Wkly Rep* 2016; 65: 993–998.
4. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci* 2003; 58(3): 249–265.
5. Duman RS. Pathophysiology of depression and innovative treatments: remodeling glutamatergic synaptic connections. *Dialogues Clin Neurosci* 2014; 16(1): 11–27.
6. Doumas M, Smolders C, Brunfaut E, et al. Dual task performance of working memory and postural control in major depressive disorder. *Neuropsychology* 2012; 26(1): 110–118.
7. Fairweather DB, Kerr JS, Harrison DA, et al. A double blind comparison of the effects of fluoxetine and amitriptyline on cognitive function in elderly depressed patients. *Hum Psychopharmacol* 1993; 8: 41–47.
8. Li X, Hamdy R, Sandborn W, et al. Long-term effects of antidepressants on balance, equilibrium, and postural reflexes. *Psychiatry Res* 1996; 63: 191–196.
9. Hallett M. Transcranial magnetic stimulation and the human brain. *Nature* 2000; 406: 147–150.
10. Janicak PG and Dokucu ME. Transcranial magnetic stimulation for the treatment of major depression. *Neuropsychiatr Dis Treat* 2015; 11: 1549–1560.
11. Janicak PG, Dunner DL, Aaronson ST, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of quality of life outcome measures in clinical practice. *CNS Spectr* 2013; 18(6): 322–332.
12. Forogh B, Ahadi T, Nazari M, et al. The effect of repetitive transcranial magnetic stimulation on postural stability after acute stroke: a clinical trial. *Basic Clin Neurosci* 2017; 8(5): 405–411.
13. Stelzel C, Bohle H, Schauenburg G, et al. Contribution of the lateral prefrontal cortex to cognitive-postural multitasking. *Front Psychol* 2018; 9: 1075.
14. Fujita N, Kunimune S and Okada S. Contribution of the dorsolateral prefrontal cortex activation, ankle muscle activities, and coactivation during dual-tasks to postural steadiness: a pilot study. *J Phys Ther Sci* 2020; 32(7): 467–472.
15. Fujita H, Kasubuchi K, Wakata S, et al. Role of the frontal cortex in standing postural sway tasks while dual-tasking: a functional near-infrared spectroscopy study examining working memory capacity. *Biomed Res Int* 2016; 2016: 7053867.
16. Teo WP, Goodwill AM, Hendy AM, et al. Sensory manipulation results in increased dorsolateral prefrontal cortex activation during static postural balance in sedentary older adults: an fNIRS study. *Brain Behav* 2018; 8(10): e01109.
17. Deschamps T, Beauchet O, Annweiler C, et al. Postural control and cognitive decline in older adults: position versus velocity implicit motor strategy. *Gait Posture* 2014; 39(1): 628–630.
18. Mignardot JB, Beauchet O, Annweiler C, et al. Postural sway, falls, and cognitive status: a cross-sectional study among older adults. *J Alzheimers Dis* 2014; 41(2): 431–439.
19. Conradi HJ, Ormel J and de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med* 2011; 41(6): 1165–1174.

20. McIntyre RS, Xiao HX, Syeda K, et al. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. *CNS Drugs* 2015; 29(7): 577–589.

21. Millan MJ, Agid Y, Brune M, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nat Rev Drug Discov* 2012; 11: 141–168.

22. Alghwiri AA. The correlation between depression, balance, and physical functioning post stroke. *J Stroke Cerebrovasc Dis* 2016; 25(2): 475–479.

23. Li Y, Wang L, Jia M, et al. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. *PLoS ONE* 2017; 12(6): e0179430.

24. Kroenke K, Spitzer RL and Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16(9): 606–613.

25. Bateni H, Collins P and Odeh C. Comparison of the effect of cane, tripod cane tip, and quad cane on postural steadiness in healthy older adults. *JPO* 2018; 30: 84–89.

26. Prieto TE, Myklebust JB, Hoffmann RG, et al. Measures of postural steadiness: differences between healthy young and elderly adults. *IEEE Trans Biomed Eng* 1996; 43(9): 956–966.

27. Duarte M and Sternad D. Complexity of human postural control in young and older adults during prolonged standing. *Exp Brain Res* 2008; 191(3): 265–276.

28. Forsman P, Haeggstrom E, Wallin A, et al. Daytime changes in postural stability and repeatability of posturographic measurements. *J Occup Environ Med* 2007; 49(6): 591–596.

29. Lafond D, Corriveau H, Hebert R, et al. Intrasession reliability of center of pressure measures of postural steadiness in healthy elderly people. *Arch Phys Med Rehabil* 2004; 85(6): 896–901.

30. Rocchi L, Chiari L and Horak FB. Effects of deep brain stimulation and levodopa on postural sway in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2002; 73: 267–274.

31. Bateni H. Postural sway in lower extremity amputees and older adults may suggest increased fall risk in amputees. *Canadian Prosthet Orthot J* 2020; 3: 33804.

32. Maki BE, Holliday PJ and Fernie GR. Aging and postural control. A comparison of spontaneous- and induced-sway balance tests. *J Am Geriatr Soc* 1990; 38: 1–9.

33. Bateni H. Changes of postural steadiness following use of prefabricated orthotic insoles. *J Appl Biomech* 2013; 29(2): 174–179.

34. Maurer C and Peterka RJ. A new interpretation of spontaneous sway measures based on a simple model of human postural control. *J Neurophysiol* 2005; 93: 189–200.

35. Doyle TL, Dugan EL, Humphries B, et al. Discriminating between elderly and young using a fractal dimension analysis of centre of pressure. *Int J Med Sci* 2004; 1(1): 11–20.

36. Massimini M, Ferrarelli F, Huber R, et al. Breakdown of cortical effective connectivity during sleep. *Science* 2005; 309: 2228–2232.