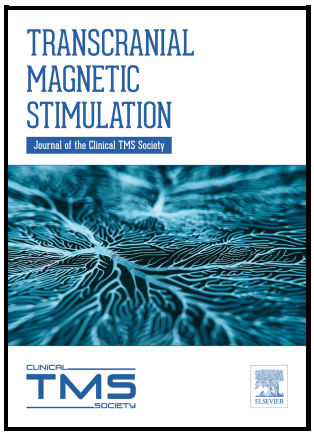

Low-Frequency Quadruple Target Transcranial Magnetic Stimulation for Severe Levodopa-Induced Dyskinesia in Parkinson's Disease. A single case report

Franco Moscovicz, Alejandro Idraste, Jose Luis Etcheverry, Jeronimo Auzmendi, Fabián Piedimonte

PII: S3050-5291(24)00081-3

DOI: https://doi.org/10.1016/j.transm.2024.100081

Reference: TRANSM100081

To appear in: *Transcranial Magnetic Stimulation*

Received date: 9 September 2024
Revised date: 10 December 2024
Accepted date: 18 December 2024

Please cite this article as: Franco Moscovicz, Alejandro Idraste, Jose Luis Etcheverry, Jeronimo Auzmendi and Fabián Piedimonte, Low-Frequency Quadruple Target Transcranial Magnetic Stimulation for Severe Levodopa-Induced Dyskinesia in Parkinson's Disease. A single case report, *Transcranial Magnetic Stimulation,* (2024) doi:https://doi.org/10.1016/j.transm.2024.100081

Low-Frequency Quadruple Target Transcranial Magnetic Stimulation for Severe Levodopa-Induced Dyskinesia in Parkinson's Disease. A single case report.

Franco Moscovicz [1, 2, 3], Alejandro Idraste [3], Jose Luis Etcheverry [3], Jeronimo Auzmendi [1,2],Fabián Piedimonte [3]

1. (CONICET), National Scientific and Technical Research Council, Buenos Aires, ARG

2. Applied Neurobiology Laboratoy, Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Instituto de Fisiopatología y Bioquímica Clínica (INFIBIOC), Buenos Aires, ARG

3. Fundación CENIT para la Investigación en Neurociencias, Buenos Aires, ARG

Corresponding author: Franco Moscovicz, francomoscovicz@gmail.com

Abstract

Levodopa-induced dyskinesias (LID) are a common and debilitating complication in patients with advanced Parkinson's disease (PD), significantly impairing quality of life. While single-target transcranial magnetic stimulation (TMS) has shown limited efficacy, multitarget approaches tailored to patient-specific symptomatology remain unexplored. Objective: This case report describes the development and application of a novel low-frequency multitarget TMS protocol designed to address severe, refractory LID in a PD patient. Methods: A 77-year-old male with advanced PD (Modified Hoehn and Yahr Stage 4) and debilitating LID underwent a personalized TMS protocol. The treatment involved 20 sessions over two weeks, targeting six cortical regions through four stimulation sites, with sequential low-frequency stimulation. Symptomatology was assessed using the Dyskinesia Diary, the Abnormal Involuntary Movement Scale (AIMS), and subjective improvement scales. Results: Dyskinesias decreased significantly, from an average of 8–10 hours per day to 2 hours daily during treatment, and were further reduced to 0–1 hour daily following a levodopa dose adjustment. Improvements persisted for up to six weeks post-treatment. The AIMS score improved from 23 (baseline) to 2 (post-treatment). Non-motor symptoms, including mood and speech articulation, also showed marked improvement. The patient reported mild, transient post-treatment rigidity and bradykinesia, which resolved with levodopa adjustments. Conclusion: This case demonstrates the potential efficacy of a multitarget low-frequency TMS protocol in managing severe LID, highlighting its role as a non-invasive alternative for patients unsuitable for deep brain stimulation (DBS). However, the findings are limited by the single-patient design, the absence of a control group, and the relatively short follow-up period. These limitations underscore the need for larger studies with sham-controlled designs and extended follow-ups to validate this approach and explore its long-term outcomes.

Keywords:

movement disorder, parkinson' s disease, dyskinesias, tms, transcranial magnetic stimulation

1. Introduction:

While levodopa has been the "gold standard" treatment for PD symptoms for more than 50 years, over time, the beneficial effects are associated with complications such as motor fluctuations and LID, a hyperkinetic movement disorder that encompasses a range of involuntary movements such as chorea, dystonia, and myoclonus, most often associated with levodopa dosing [1]. These symptoms typically worsen in stressful situations and significantly impair the quality of life of affected individuals. These complications occur in a variable spectrum of severity and affect most, if not all, patients during the progression of the disease. The pathophysiology of LID is complex, involving both modifiable factors (e.g., levodopa dose) and non-modifiable factors (e.g., age, disease duration, genetic predisposition) [2,3]. Since it is not the purpose of this article to delve into this complexity, more information on dyskinesias and their management can be found in articles such as Heumann et al. (2014), which provide detailed context on risk factors, presentation, physiopathology, types, and subtypes [4,5]. However, as more classical therapeutic approaches, such as adjusting dopaminergic medication or implementing structured physical therapy programs, are often insufficient in providing relief, particularly in severe cases, new treatment modalities deserve greater attention.

For those patients unresponsive to pharmacological and physical management, neuromodulation techniques, such as invasive deep brain stimulation (DBS) and non-invasive TMS, offer promising alternatives. While DBS is an effective and widely used treatment for refractory movement disorders, it involves increasingly lower, yet still significant, surgical risks and is limited to carefully selected patients due to its complexity, cost, and potential side effects [6]. In contrast, TMS provides a non-invasive less explored alternative with a robust safety profile, making it particularly relevant for patients who are not ideal candidates for invasive procedures. Furthermore, TMS is programmable and adjustable, allowing for the development of tailored protocols based on the severity and clinical particularities of the patient. Moreover, recent advancements have introduced personalized target site selection based on person-specific brain network architecture, as summarized in a comprehensive review by Cash and Zalesky [7].

TMS works by generating an electromagnetic field from a coil placed on the patient's scalp, which induces an electric current in specific areas of the brain, modulating neuronal activity [8]. Its applications range from depression and PTSD to chronic pain, movement disorders, and an expanding spectrum of diseases and symptoms [9,10,11]. Despite its widespread use, most TMS protocols for PD and LID have focused on single-target approaches. One of the most frequently targeted areas is the supplementary motor area (SMA). The rationale behind this target is supported by its long-recognized impairment in dyskinetic PD patients, which likely contributes to LID through imbalances in basal ganglia-cortical circuitry [12]. Low-frequency

rTMS (1 Hz) over the SMA has been shown to transiently reduce dyskinesias by inducing cortical inhibition, without affecting motor performance [13,14]. On the other hand, the primary motor cortex (M1) target has been shown to modulate motor cortical excitability and improve dyskinesia and dystonia scores, with evidence suggesting beneficial effects when applied across multiple sessions [15]. While these targets have demonstrated potential in alleviating symptoms, they may not fully address the diverse presentations of dyskinesias, highlighting the need for innovative therapeutic designs, including the possibility of combining multiple neuromodulation regions to achieve broader clinical benefits.

The single-target approach is partly practical in clinical studies due to the challenge of attributing therapeutic effects to individual targets in multi-target studies. However, recent trials suggest that combining multiple targets tailored to the patient's symptomatology could be highly effective, opening new avenues for patient-directed therapies based on clinical presentation. For example, a recent review highlights how TMS protocols can be individualized to address the diverse symptomatic presentations of multiple sclerosis, a disease that also shares heterogeneity in clinical manifestations [16]. This rationale aligns closely with the concept of applying multi-target TMS in movement disorders like Parkinson’s disease.

In this context, and utilizing the existing literature and protocols reported to date(13,14,15), we developed a novel multitarget low-frequency TMS protocol tailored to the specific symptomatology of a patient with severe LID. The decision to use low-frequency stimulation (1 Hz) was based on evidence from Shirota et al. (2013), which demonstrated the long-lasting efficacy of low-frequency repetitive TMS (rTMS) over the supplementary motor area (SMA) in improving motor symptoms in Parkinson’s disease compared to other stimulation frequencies [17]. Unlike conventional single-target protocols, this approach aimed to modulate multiple functional areas of the brain while adhering to established safety guidelines [18]. This protocol was specifically designed considering the severity of the patient’s symptoms, their impact on quality of life, the lack of alternative therapeutic options, and the unsuitability of DBS due to high surgical risk. By targeting six specific regions (bilateral primary motor areas for upper and lower limbs and the supplementary motor area) using four stimulation targets, we sought to explore the therapeutic potential of individualized, high-dose multitarget TMS in addressing both motor and non-motor symptoms in a patient with severe refractory dyskinesias. This report presents the outcomes of this intervention, providing a foundation for further studies on patient-specific TMS protocols.

2. Case Presentation

A 77-year-old male patient had been diagnosed with PD 15 years prior to his referral to the TMS Cenit Foundation Service for evaluation. Over recent years, his disease progression significantly worsened. After a prolonged period of effective control with medication, he developed severe LID, which compromised his postural stability and led to recurrent falls. These complications severely impaired his ability to perform daily activities, resulting in a profoundly diminished quality of life.

The patient experienced debilitating dyskinetic movements with his current levodopa dose. Attempts to lower the dosage worsened bradykinesia and freezing episodes, further compromising gait stability. His symptoms included retrocollis, generalized choreiform movements, and dystonic activity affecting the lower limbs, upper limbs, torso, and larynx. These were present bilaterally during both “on” and “off” periods, with notable exacerbations during “on” periods (2–3 hours of wearing off). Additionally, the patient exhibited involuntary perioral movements, impaired speech, constant sialorrhea, sleep behavior disorder, and a partial inability to communicate verbally. On the Modified Hoehn and Yahr Scale, the patient was classified as Stage 4.

The most severe consequences of the LID included a sternal fracture and multiple head contusions from falls. At the time of his referral, the patient demonstrated a marked decline in functionality and reported significant suffering. His medication regimen included Levodopa/Benserazide (200 mg/50 mg) taken every three hours (five doses daily, total 1000 mg/day), Amantadine (100 mg), three times a day, and Clonazepam (0.25 mg) in the afternoon and before sleep.

During the physical examination, generalized dyskinetic movements were confirmed, affecting all four limbs, torso, head, and speech articulation. The patient experienced approximately eight hours of active dyskinesias daily, with an Abnormal Involuntary Movement Scale (AIMS) score of 23. Laboratory values were within normal ranges. The patient was evaluated for deep brain stimulation (DBS) but was not considered a candidate due to the age-related high surgical risk [6].

3. Treatment

Given the severity of the condition and the lack of alternative therapeutic options, and after explaining to the patient the potential benefits and risks of the treatment and obtaining their written informed consent, a novel low-frequency, multitarget TMS protocol based on the existing protocols reported to date(13,14,15), that adhered to established safety guidelines (18) was designed and implemented. The MagVenture MagPro R30 device with a figure-8 Cool-B70 coil was used for stimulation. The protocol included two daily sessions, separated by one hour, of sequential low-frequency biphasic stimulation (1 Hz) targeting six specific regions across four stimulation targets over two weeks, with each target stimulated for 20 minutes during a session, totaling 40 minutes per session The total treatment regimen consisted of 20 sessions, delivering 4800 pulses per day at 110% of the resting motor threshold. These regions included the bilateral primary motor cortices for upper and lower limbs (counted as one target for lower limbs due to the possibility of bilateral stimulation achieved by placing the coil sagittally) and the supplementary motor area (SMA) (Fig. 1A and B).

To determine the resting motor threshold, the minimal amplitude required to elicit a visible movement of the first dorsal interosseous muscle of the hand was observed. Each target was located using the corresponding motor response as follows: for the M1 targeting the upper limbs, the first dorsal interosseous muscle was used; for the M1 targeting the lower limbs, visible twitching of the tibialis anterior muscles was assessed through palpation; and for the SMA, the coil was placed 3 cm anterior to Cz of the 10–20 EEG system in the sagittal midline, allowing simultaneous stimulation of the SMA in both hemispheres, as previously described (13). Supra-threshold (110%) intensity was employed also to ensure precise coil placement, continuously monitored by a specialized technician throughout the procedure.

4. Evaluation Metrics

Three types of scales were used to measure symptomatology:

Dyskinesia Diary: The number of hours of active dyskinesias was measured daily, starting one week before treatment and continuing for five weeks after the treatment ended (eight weeks in total). These recordings were collected to monitor the immediate and sustained effects of the intervention (Fig. 2A and B).

AIMS Score: Evaluations using the Abnormal Involuntary Movement Scale (AIMS) were conducted on the Friday before treatment and on three consecutive Fridays after the start of treatment to measure the severity of dyskinetic movements objectively (19)(Fig. 2C).

Subjective Improvement Scales: The patient and caregiver evaluated the five most disabling symptoms weekly using a subjective improvement scale. This scale ranged from 0 (symptoms unchanged from the week prior to treatment) to 100 (maximum improvement expected). Overall perceived improvement was also assessed during and after treatment (Fig. 3).

5. Results:

5.1 Reduction in Dyskinesias

Dyskinesias decreased significantly from the first day of treatment, with a reduction from an average of 8–10 hours daily to an average of 2 hours daily during the two weeks of treatment and the subsequent week. After reducing the levodopa dosage by 200 mg/day, the improvement was sustained, with dyskinesias reduced to 0–1 hour per day for six weeks, persisting until the final evaluation (Fig. 2A and B). The medication regimen required only one adjustment, which had been pre-established as a possible

measure at the start of treatment and was implemented on the third day following the completion of therapy. This adjustment was motivated by two factors: the symptomatic improvement in non-motor domains, which suggested greater safety for Levodopa dose reduction, and the reappearance of dyskinetic movements on days 2 and 3 post-treatment (see Fig. 2A).

The new medication regimen consisted of one less dose of Levodopa/Benserazide (200 mg/50 mg). Administered every 4 instead of 3 hours (four doses daily, totaling 800 mg/day), Amantadine (100 mg) three times daily, and Clonazepam (0.25 mg) in the afternoon and before sleep. This regimen achieved a prolonged effect of levodopa, maintaining an extended "ON" period without dyskinesias.

Across the eight-week observation period, the frequency of dyskinesias (measured as hours of active dyskinesias/awake hours per day) decreased substantially. Starting from a baseline of 52.68% in Week 1 (pre-treatment), the frequency dropped to 12.50% in Week 2, demonstrating a rapid and marked improvement. This trend continued with further reductions to 2.68% in Week 3, followed by a slight increase to 5.31% in Week 4. An optimal state with no dyskinesias (0.00%) was achieved in Week 5. Minor increases occurred in Week 6 (4.46%) and Week 8 (6.25%), but these remained markedly lower than baseline levels (Table 1).

5.2 Changes in AIMS Score

Before starting treatment, the patient's AIMS score was 23, reflecting severe dyskinetic movements. Following the first week of treatment, the score decreased to 11, then to 4 in the second week, and finally to 2 in the third week. This marked a drastic and sustained improvement in dyskinesia severity (Fig. 2C).

5.3 Subjective Improvements

The patient and caregiver reported significant improvements in all parameters evaluated weekly, particularly in functional abilities and overall quality of life (Fig. 3). Notably, the patient reported a 75% medium reduction in the most disabling symptoms by the end of the second week of treatment, which was maintained through the follow-up period.

5.4 Reported Side Effects

During the two weeks following treatment, the patient reported mild increases in rigidity and bradykinesia, which had not been present prior to the intervention. The onset of rigidity and bradykinesia was primarily noted during the first six days post-treatment and was also associated with the previously mentioned recurrence of dyskinetic movements on days 1, 2, and 3 after the treatment (Fig. 2A). Collectively, these symptoms manifested as "ON" periods with the appearance of dyskinetic movements and "OFF" periods characterized by episodes of rigidity. This presentation differed from the pre-

treatment state, where the patient reported dyskinesias during both "ON" and "OFF" periods. These symptoms gradually diminished after the third week, paradoxically following a 200 mg reduction in the total daily levodopa intake on the third-day post-treatment. Achieving longer ON periods without the appearance of dyskinesias and without OFF periods characterized by rigidity.

6. Discussion

This case report highlights the successful application of a novel quadruple-target TMS protocol, achieving a substantial and sustainable reduction in severe LID in a PD patient. The treatment not only effectively reduced dyskinesias from an average of 8–10 hours daily to nearly zero but also brought significant improvements in the patient's overall quality of life. Enhancements were observed in gait, speech articulation, and mood, collectively contributing to better daily functioning and subjective well-being.

The dramatic reduction in dyskinesias aligns with findings from studies demonstrating TMS's ability to modulate neuronal circuits involved in hyperkinetic disorders [20, 21]. The sustained improvement over a six-week follow-up period is particularly notable given the advanced stage of the disease and the absence of alternative treatment options.

The rationale for adopting a multitarget approach stems from the heterogeneity and severity of the dyskinesias in this patient, likely involving multiple interconnected brain regions. Moreover, this protocol adheres to recent advancements in neuromodulation techniques therapy, which emphasize personalized treatment tailored to the patient's specific symptomatology and disease severity as also seen in the target selection in DBS [6].

As DBS is widely regarded as a highly effective treatment for refractory movement disorders, with well-documented long-term benefits in alleviating both motor and non-motor symptoms of PD it requires invasive surgery, which, despite advances in techniques, still carries significant risks such as infection, hemorrhage, or hardware-related complications. Moreover, not all patients are suitable candidates for DBS, particularly those with advanced age, significant comorbidities, or contraindications to surgery [22].

In contrast, TMS offers a non-invasive and safer alternative with a robust safety profile, particularly in patients unsuitable for surgical interventions. However, its effects are generally less durable compared to DBS, often requiring maintenance sessions, and its efficacy for severe and complex dyskinesias is still under investigation. Additionally, logistical challenges, such as the need for frequent sessions in multitarget protocols, may limit accessibility and feasibility in certain clinical settings.

While the results of this single case were overwhelmingly positive in this particular case, the emergence of increased rigidity and bradykinesia post-treatment warrants attention. These side effects, which resolved after adjusting the levodopa dosage, highlight the delicate balance required when managing motor symptoms in advanced PD. For this observation is recommendable the work of Vijayakumar et al. (2016), who emphasized the importance of tailoring interventions to minimize adverse effects while optimizing therapeutic outcomes [23].

Despite its promising results, this study has several limitations. As a single case report, the findings lack generalizability and must be interpreted with caution. The absence of a control group further complicates the attribution of outcomes solely to the TMS intervention, as placebo effects or natural symptom fluctuations could also play a role. Nonetheless, this report serves as a critical proof of concept, demonstrating the feasibility and potential efficacy of tailored multitarget TMS protocols in severe LID.

Future research should aim to address these limitations through larger randomized controlled trials with sham stimulation conditions to validate these findings. Additionally, exploring the long-term durability of these effects and their applicability to a broader range of PD patients will be crucial. Combining TMS with other therapeutic interventions, such as pharmacological treatments or physical therapy, may also offer synergistic benefits and should be investigated further.

Finally, advancements in neuromodulation technology, including home-based devices and neuronavigation-guided stimulation, could improve the accessibility and practicality of multitarget TMS. Emerging approaches such as transcranial static magnetic stimulation (tSMS) may provide simpler, cost-effective alternatives, particularly for patients unable to access conventional TMS centers [23].

Conclusion

This case report demonstrates that a novel, multitarget TMS protocol can significantly reduce severe LID and improve overall quality of life in a PD patient. These findings highlight the importance of individualized treatment strategies and suggest a way for further research into the role of personalized TMS protocols in managing complex movement disorders. While the results are promising, larger studies are essential to validate this approach and explore its broader applicability.

References

1. Fahn S: Parkinson Disease, the Effect of Levodopa, and the ELLDOPA Trial . Arch Neurol. 1999, 56:529-535. 10.1001/archneur.56.5.529

2. LeWitt PA, Fahn S: Levodopa therapy for Parkinson disease: A look backward and forward . Neurology. 20168614, 1:3-12. 10.1212/WNL.0000000000002509
3. Athulya RT, Jayakrishnan S, Iype T, et al.: Predictors of Levo-dopa induced Dyskinesias in Parkinson's Disease. Annals of Indian Academy of Neurology . 2020, 10.4103/aian.AIAN_460_18
4. Heumann, Rolf et al. “Dyskinesia in Parkinson's disease: mechanisms and current non-pharmacological interventions.” *Journal of neurochemistry* vol. 130,4 (2014): 472-89. doi:10.1111/jnc.12751
5. Bezard E, Brotchie J, Gross C: Pathophysiology of levodopa-induced dyskinesia: Potential for new therapies . Nat Rev Neurosci. 2:577-588.
6. Dallapiazza RF, De Vloo P, Fomenko A, et al. Considerations for Patient and Target Selection in Deep Brain Stimulation Surgery for Parkinson’s Disease. In: Stoker TB, Greenland JC, eds. *Parkinson’s Disease: Pathogenesis and Clinical Aspects*. Brisbane (AU): Codon Publications; December 21, 2018.
7. Cash, Robin F H, and Andrew Zalesky. “Personalized and Circuit-Based Transcranial Magnetic Stimulation: Evidence, Controversies, and Opportunities.” *Biological psychiatry* vol. 95,6 (2024): 510-522. doi:10.1016/j.biopsych.2023.11.013
8. Terao, Y., Ugawa, Y., 2002: Basic Mechanisms of TMS. Journal of Clinical Neurophysiology. 19:322. 10.1097/00004691-200208000-00006
9. Lefaucheur JP, Aleman A, Baeken C, et al.: Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018).. Clin Neurophysiol . 2020, 2014:474-528.
10. Grisaru N, Amir M, Cohen H, et al.: Effect of transcranial magnetic stimulation in posttraumatic stres disorder: a preliminary study. Biological Psychiatry. 44:52-55. 10.1016/s0006-3223(98)00016-x
11. Fernandes AM, Graven-Nielsen T, de Andrade DC, et al.: New updates on transcranial magnetic stimulation in chronic pain. Curr Opin Support Palliat Care. 16:65-70.
12. Playford, E D et al. “Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study.” *Annals of neurology* vol. 32,2 (1992): 151-61. doi:10.1002/ana.410320206
13. Koch G, Brusa L, Caltagirone C, et al.: rTMS of supplementary motor area modulates therapy-induced dyskinesias in Parkinson disease. Neurology. 2005, 23:623-5. 10.1212/01.wnl.0000172861.36430.95.
14. Sayın S, Cakmur R, Yener G, et al.: Low-frequency repetitive transcranial magnetic stimulation for dyskinesia and motor performance in Parkinson’s disease. J Clin Neurosci. 21:1373-1376.

15. Filipović SR, Rothwell JC, van de Warrenburg BP, et al.: Repetitive transcranial magnetic stimulation for levodopa-induced dyskinesias in Parkinson's disease. Mov Disord. 2009, 24:246-253. 10.1002/mds.22348
16. Zhou X, et al. (2022). "Clinical application of transcranial magnetic stimulation in multiple sclerosis". Frontiers in Immunology. DOI: 10.3389/fimmu.2022.902658
17. Shirota, Yuichiro et al. "Supplementary motor area stimulation for Parkinson disease: a randomized controlled study." *Neurology* vol. 80,15 (2013): 1400-5. doi:10.1212/WNL.0b013e31828c2f66
18. Rossi S, Antal A, Bestmann S, et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. *Clin Neurophysiol*. 2021;132(1):269-306. doi:10.1016/j.clinph.2020.10.003
19. Gharabawi GM, Bossie CA, Lasser RA, et al.: Abnormal Involuntary Movement Scale (AIMS) and Extrapyramidal Symptom Rating Scale (ESRS): cross-scale comparison in assessing tardive dyskinesia. Schizophr Res. 2005, 77:119-28. 10.1016/j.schres.2005.03.008.
20. Latorre A, Rocchi L, Berardelli A, et al.: The use of transcranial magnetic stimulation as a treatment for movement disorders: A critical review.. 2019, 10.1002/mds.27705.
21. Somaa FA, de Graaf TA, Sack AT.: Transcranial Magnetic Stimulation in the Treatment of Neurological Diseases. . Front Neurol.. 2022, 10.3389/fneur.2022.793253.
22. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol*. 2011;68(2):165. doi:10.1001/archneurol.2010.260
23. Vijayakumar D, Jankovic J.: Drug-Induced Dyskinesia, Part 1: Treatment of Levodopa-Induced Dyskinesia. . Drugs.. 2016, 10.1007/s40265-016-0566-3.
24. Pagge, C., Caballero-Insaurriaga, J., Oliviero, A. *et al.* Transcranial static magnetic field stimulation of the supplementary motor area decreases corticospinal excitability in the motor cortex: a pilot study. *Sci Rep* **14**, 6597 (2024). https://doi.org/10.1038/s41598-024-57030-0

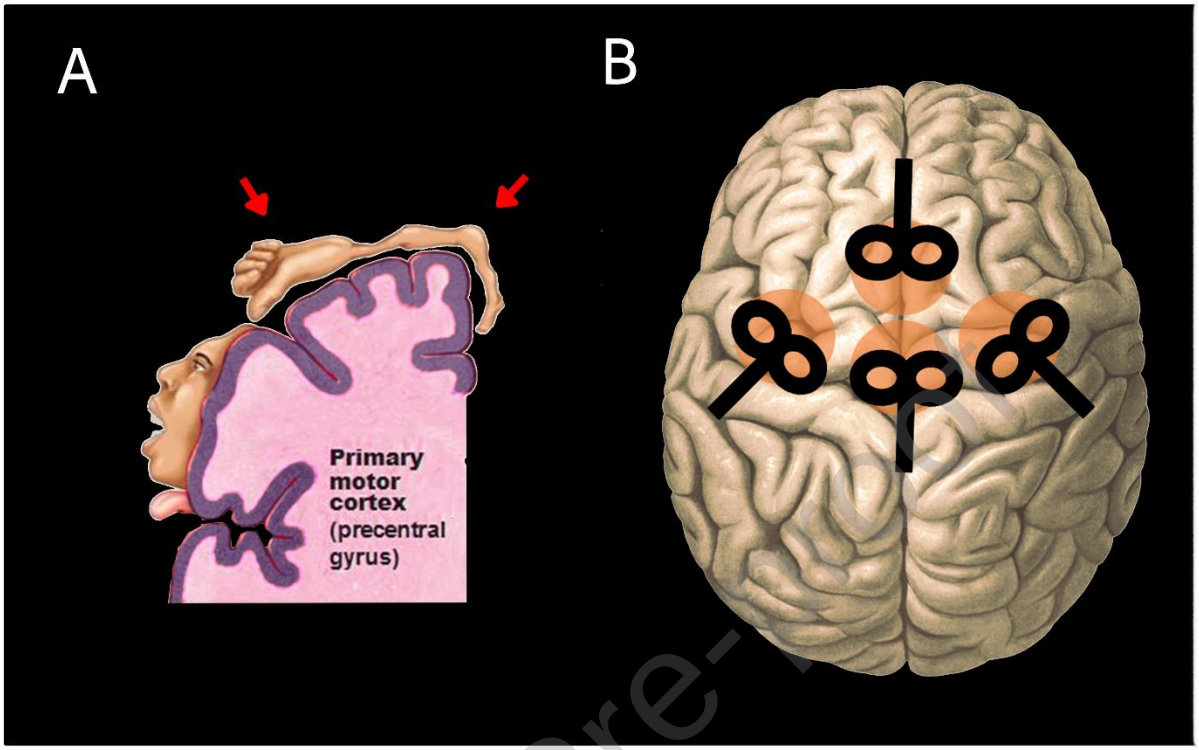

FIGURE 1: Schematic TMS protocol design

A. Motor Homunculus: Somatotopic organization of the primary motor cortex (precentral gyrus). The diagram illustrates the anatomical regions corresponding to different body parts, with red arrows indicating the specific areas targeted for TMS treatment. B. Schematic representation of targets: A diagrammatic illustration of the four target areas on the brain's surface used during TMS treatment. Each target is depicted with a circular mark, highlighting the precise stimulation locations. Image Credits: First Author.

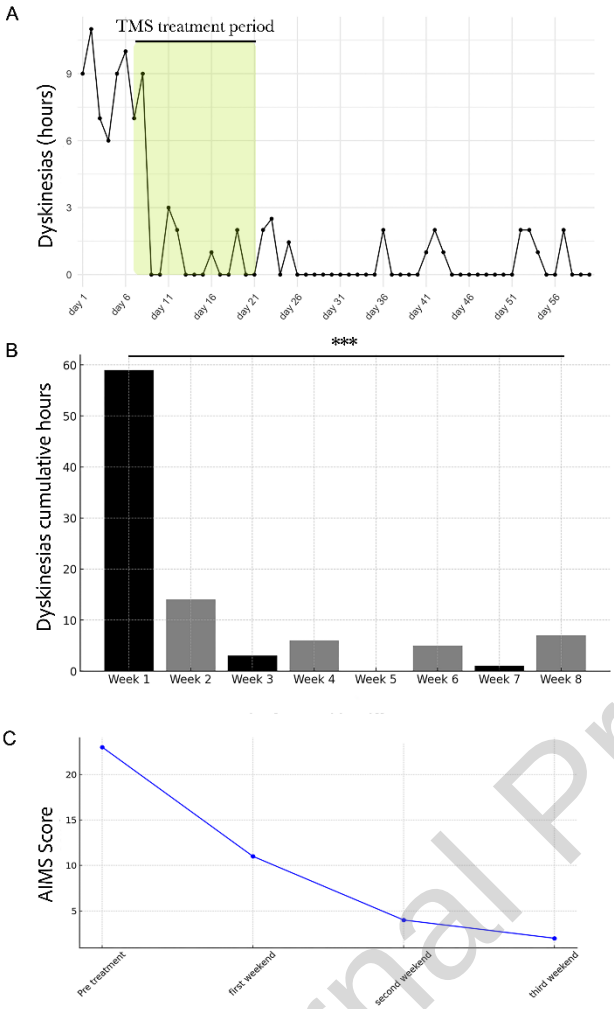

FIGURE 2: Daily Dyskinesias Diary and AIMS score evolution

A. Daily hours of dyskinesias recorded over 60 days. The y-axis shows the hours of dyskinesias experienced each day. The green shaded area highlights the period during which TMS treatment was administered. B. Weekly Hours Accumulated of Dyskinesias Over Eight Weeks: This bar graph compares the weekly accumulated hours of dyskinesias over eight weeks. Statistical analysis indicates significant differences in dyskinesias between the first week (pre-treatment) and the following weeks, '***' Indicates a significant difference by the Student's t-test ($P < 0.01$). C. Abnormal Involuntary Movement Scale (AIMS) score evolution over and after the treatment.

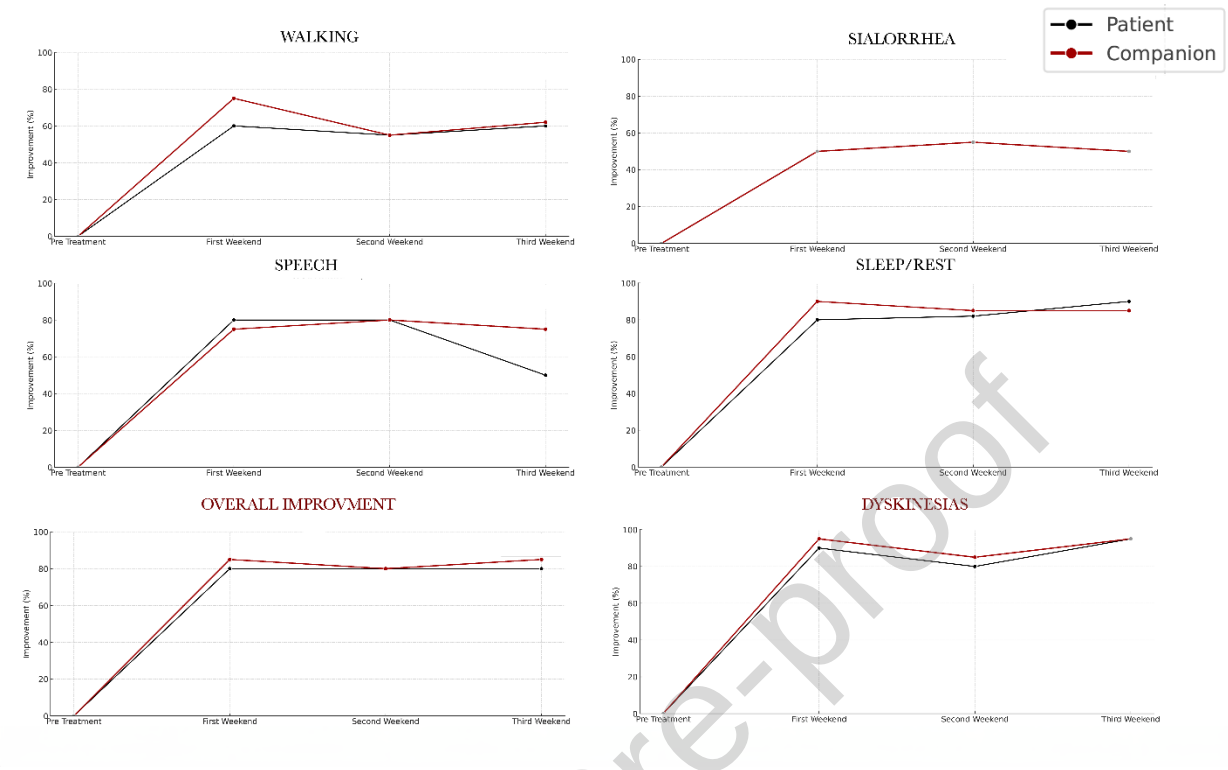

FIGURE 3: Symptomatic Subjective Scales Over Treatment

Subjective improvement in five key symptoms (Walking, Sialorrhea, Speech, Sleep/Rest, and Dyskinesias) along with Overall Improvement as reported by both the patient and their companion throughout three weekends intra and after-treatment

TABLE 1: Weekly Frequency of Dyskinesias

Week	Total Dyskinesias Hours	Frequency of Dyskinesias
1	59	0.527 (52.68%)
2	14	0.125 (12.5%)
3	3	0.027 (2.68%)
4	5.95	0.053 (5.31%)
5	0	0 (0%)
6	5	0.045 (4.46%)
7	1	0.009 (0.89%)
8	7	0.062 (6.25%)

This table shows the updated weekly hours accumulated with dyskinesias and their frequency relative to the total weekly awake hours (16 hours per day). The frequency of dyskinesias is represented as a proportion of the total weekly awake hours, providing a clearer picture of the patient's condition over time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.