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Effects of Transcranial Pulse Stimulation (TPS) as a potential "add-on" intervention in patients with Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative movement disorder characterized by symptoms such as resting tremor, bradykinesia, and rigidity. Non-motor symptoms are also evident, such as depression, anxiety and sleep problems. Even if pathogenesis of PD still needs to be exhaustively identified, new evidence is increasingly available to improve management of PD symptoms, trying to slow its progression. In this context, Non-Invasive Brain Stimulation (NIBS) is one of the most investigated fields, continuously offering new solutions and techniques. In this regard, Transcranial Pulse Stimulation (TPS) is a novel/painless/safe method that exploits mechanical effects induced by shock waves: TPS may act on mechano-sensitive ion channels, transducing mechanical stimuli into bio-chemical signals and triggering a cascade of responses that may result in supra-threshold firing of stimulated neurons. Compatibly, this process may lead to changes in neurotransmitters such as dopamine, serotonin, and γ-aminobutyric acid (GABA). TPS has been recently approved as a potential intervention for treating cognitive decline in Alzheimer's Disease patients. On this line, very recent data suggest a possible and novel improvement effect also for motor symptoms of PD (please refer to Supplementary Materials for references and details). As a consequence, in the present work, we proposed an "off-label"/"add-on" TPS treatment to a cohort of PD patients for a better management of their symptoms. Evidence of clinical scores (e.g., motor scales, resting tremor, and quality of life) are reported, also comprising follow-up evaluations. Specific eligibility criteria were established for TPS administration, such as a confirmed diagnosis of idiopathic PD according to the International Parkinson and Movement Disorder Society criteria, and presenting a "tremor-dominant" phenotype (please refer to Supplementary Materials for a more exhaustive description of exclusion/inclusion criteria). Ten participants (52–76 years; 6 males, 4 females) were thus evaluated before and after an "off-label" TPS treatment. Considering the intention to exploit TPS as an "add-on" therapy, patients were always assessed/treated while in their pharmacological "ON" state (i.e. about 2 h after the last drug intake). This study was approved by the relevant Institutional Review Board, adhering to ethical standards of the Declaration of Helsinki. Patients signed an informed consent, allowing them to withdraw at any time from the intervention without affecting their ongoing treatment.

TPS was administered using Neurolith© (Storz Medical AG, Tägerwilen, Switzerland). Stimulation was set at a frequency of 4 Hz and an energy level of 0.20 mJ/mm^2. Each participant underwent four TPS sessions over a two-week period (two sessions in a week). In each session, 1500 pulses were applied to the motor cortex contralateral to the most affected body side (e.g., if symptoms were predominant in the right side, stimulation was targeted to the left motor cortex). Each session lasted approximately 30 minutes and consisted of three blocks of 500 pulses, with 5-min breaks between blocks. Clinical and demographic data were collected: evaluations were conducted using the Unified Parkinson's Disease Rating Scale (UPDRS), including Part I (assessment of mental status, behavior and mood), Part II (self-assessment of sensorimotor experiences of daily living), Part III (clinical motor examination), and Part IV (clinical evaluation of motor/non-motor complications). In the case of UPDRS-III, attention was also given to tremor-related sub-scores to better assess motor impairments. Scores were evaluated before the first TPS session (baseline, T0), immediately after the end of treatment (T1), and two weeks after the end of treatment (follow-up, T2). Finally, to assess potential effects of TPS on quality of life, the Parkinson's Disease Questionnaire-8 (PDQ-8) was administered at T0 and T2 to evaluate possible changes in patients' lifestyle and daily functioning resulting from treatment. We also evaluated resting tremor severity by means of an accelerometer connected to an electromyography (EMG) system (Natus Synergy, Synopo, Italy) that was used to measure tremor amplitude on the most affected side of the body (i.e. contralateral to TPS administration on motor cortex). Recordings were obtained at T0, T1, and T2. Finally, at T1 and T2, participants were asked to complete a visual analog scale ranging from 0 ("no improvement") to 10 ("maximal improvement") to subjectively rate any perceived changes in tremor, rigidity, and bradykinesia (in comparison to baseline conditions). Please refer to Supplementary Materials for further details about methods. No relevant side effects were reported after TPS administration, as verified by unstructured interviews administered after every stimulation session and at every post-intervention evaluation. Patients resulted in significant clinical improvements (at T1 and T2, in comparison to baseline) when considering the UPDRS total score (obtained from the sum of the considered parts), UPDRS-III (and sub-scores related to tremor), and accelerometer data (especially at T1; see Fig. 1). Similarly, PDQ-8 significantly improved at

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T2, while qualitative evaluation of motor improvements showed significant amelioration in resting tremor only (at T1 and T2). Please refer to Supplementary Materials for detailed statistics (and correlations), as well as for complete clinical/demographic characteristics of patients.

In the present work, on the basis of Manganotti et al. [1] suggesting positive effects of TPS on PD symptoms with respect to sham stimulation after a single-session, we realized an "off-label"/"open-label" work in which 4 TPS sessions were foreseen in two weeks. TPS administration on motor cortex of PD patients resulted in improved clinical scores, (especially) as evaluated by means of the UPDRS total score and the UPDRS-III score (clinical motor examination). Furthermore, patients resulted in lower levels of resting tremor. Patients also reported a general improvement in quality of life and qualitative motor improvements (especially when considering behaviours related with resting tremor). As in Manganotti et al. [1], findings suggest that TPS was useful for improving motor symptoms in PD patients (also at follow-up), with particular reference to resting tremor. Tremor could be defined as an involuntary and rhythmic oscillatory movement, and is a hallmark motor symptom of PD. Its pathophysiology is complex: the "oscillator hypothesis" suggests that pathological oscillations within specific brain networks such as the cortico-basal-thalamo-cortical and cerebello-thalamo-cortical circuits may drive the main contributions to it [2,3]. Compatibly, neuromodulatory interventions like Deep Brain Stimulation and repetitive Transcranial Magnetic Stimulation have shown a good efficacy in interacting with these circuits and alleviating symptoms [4,5]. Recently, also TPS as a novel/non-invasive/well-tolerated technique has emerged as a potential treatment option. Here, we confirmed and expanded this evidence, suggesting that improvements in motor scores may be especially evident in resting tremor (likely interacting with cortico-basal-thalamo-cortical/cerebello-thalamo-cortical circuits) also after about two weeks from the end of treatment. In conclusion, even taking in account limitations of the present report (such as the utilization of a non-randomized/non-controlled and open-label design, and a small sample size), TPS may be a promising tool that may be used in addition to classical interventions (i.e., pharmacological and/or physical treatment) to allow a better control/management of PD symptoms. In this context, a larger randomized, sham-controlled trial may be the most appropriate design to further validate TPS as a possible "add-on" intervention in PD.

CRediT authorship contribution statement

Paolo Manganotti: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marco Liccari:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Tiziana Maria Isabella Lombardo:** Writing – review & editing, Investigation. **Jacopo Della Toffola:** Writing – review & editing, Validation, Formal analysis. **Valentina Cenacchi:** Writing – review & editing, Investigation. **Miloš Ajčević:** Writing – review & editing, Formal analysis. **Mauro Catalan:** Writing – review & editing, Conceptualization. **Pierpaolo Busan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis.

Data statement

Data are available upon reasonable request to the Corresponding Author.

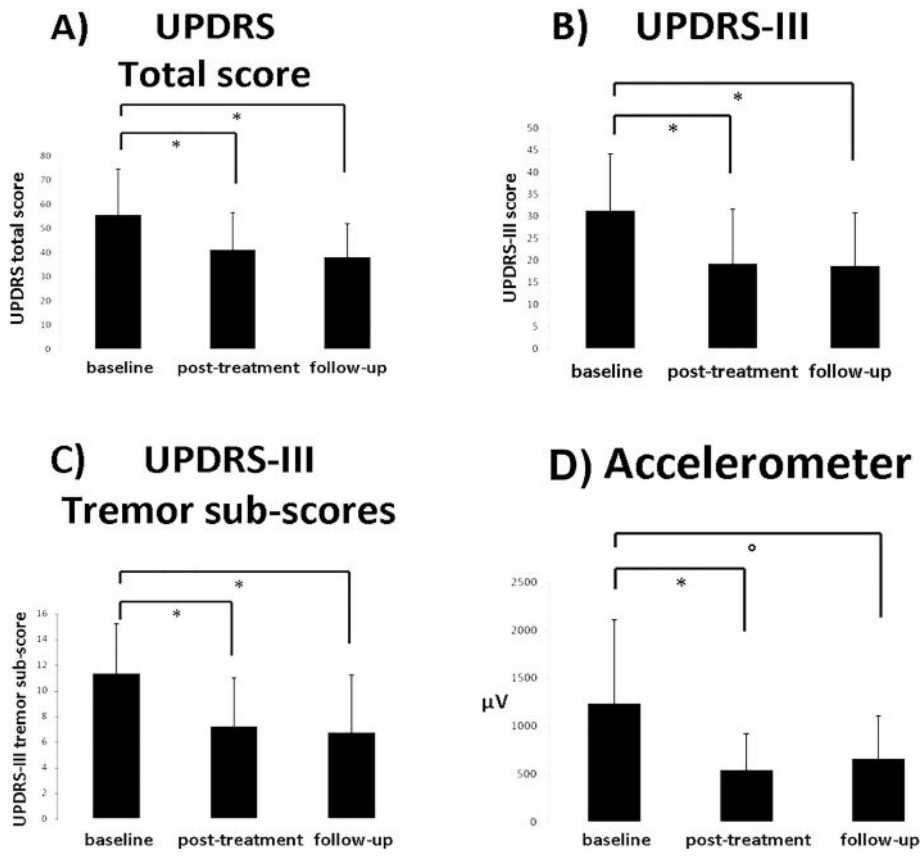

Fig. 1. Representation of main findings obtained from UPDRS scale. A) UPDRS total scores obtained at baseline, post-treatment and follow-up; B) UPDRS-III scores obtained at baseline, post-treatment and follow-up; C) UPDRS-III tremor sub-scores obtained at baseline, post-treatment and follow-up; D) Accelerometer recordings obtained at baseline, post-treatment and follow-up. Comparisons that resulted in significant differences are marked with an asterisk (*) while statistical trends are indicated with a circle (°).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Paolo Manganotti reports that equipment (and supplies) was provided by Storz Medical AG, Tägerwilen, Switzerland. All the other 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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2025.108128.

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