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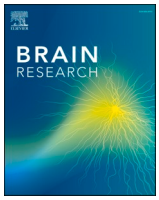

# Effect of a single session of transcranial pulse stimulation (TPS) on resting tremor in patients with Parkinson's disease

ARTICLE INFO

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ABSTRACT

*Introduction:* Tremor is a common symptom in movement disorders and is evident at rest in Parkinson's Disease (PD). In PD, tremor may be responsive to brain stimulation, ranging from Deep Brain Stimulation to Transcranial Magnetic Stimulation. Transcranial Pulse Stimulation (TPS) is a novel/painless/non-invasive technique which appears to induce biomolecular changes through shock waves. Here, as one of the first studies in the field of PD, we exploratively investigate the possibility to observe changes in tremor, induced by single-session TPS delivered on the motor cortex of PD patients.

*Methods:* TPS was delivered in 16 patients. Of these, 9 were admitted to sham (placebo). Resting tremor was measured at baseline (T0), after TPS (T1), and after 24 h from intervention (T2).

*Results:* At baseline, tremor was always present. After TPS, tremor reduction was noted at T1 and T2 (compared to T0 and placebo). We noted a decrease in the amplitude of resting tremor (not its frequency).

*Discussion:* TPS is a non-invasive technique that may be a novel solution for reducing tremor in PD, lasting at least 24 h after single-sessions. No side effects were reported. We discuss evidence suggesting potential physiological changes in mechanisms of neural circuits that are affected in PD.

## 1. Introduction

Tremor is a common movement disorder, typically defined as an "*involuntary, rhythmic, oscillatory movement of a body part*" (Deuschl et al., 2001; Deuschl and Bergman, 2002). Tremor is considered a complex syndrome, with various subtypes and distinct pathophysiological mechanisms. Importantly, tremor at rest is one of the cardinal motor signs of Parkinson's Disease (PD; Bhatia et al., 2018). However, its phenomenology, pathophysiology, and treatment are highly complex (compare with Helmich et al., 2013; Dirkx et al., 2017; van der Stouwe et al., 2020; Chen et al., 2022; Dirkx and Bologna, 2022). Many models have been proposed to elucidate the possible pathophysiology of tremor. One influential model, relevant to all syndromes characterized by this symptom, is the "*oscillator hypothesis*", which posits that biological systems can result in abnormal (neural) oscillatory activity under certain (pathological) conditions, thus manifesting tremor at the clinical level (Deuschl et al., 2001; Deuschl and Bergman, 2002). More specifically, four potential mechanisms have been suggested, leading to the appearance of this abnormal pattern: a) mechanical properties of the body parts; b) stretch reflexes in the extremities; c) oscillatory properties of neurons in affected brain regions, and, as a consequence, d) oscillatory neural activity that occurs when feedforward or feedback systems involving brain regions such as the cerebellum become unstable (see Deuschl and Bergman, 2002; compare with Helmich et al., 2013; Dirkx et al., 2017; van der Stouwe et al., 2020; Dirkx and Bologna, 2022). With regards to central (i.e. neural) oscillators, abnormal rhythmic activity may be generated within specific brain regions and propagated through networks that could be critical for tremor appearance. For instance, the cortico-basal-thalamo-cortical and the cerebello-thalamo-cortical motor networks may both play a role in the pathological mechanisms underlying (PD-induced) resting tremor (compare with Deuschl et al., 2001; Deuschl and Bergman, 2002; Helmich et al., 2013; Dirkx et al., 2017; van der Stouwe et al., 2020; Dirkx and Bologna, 2022).

Resting tremor in Parkinson's Disease (PD) is highly responsive to brain stimulation protocols, as demonstrated by evidence from clinical experience and (invasive) techniques such as Deep Brain Stimulation (DBS; Bronstein et al., 2011; Oswal et al., 2016) or (non-invasive) solutions such as Transcranial Magnetic Stimulation (TMS; Frey et al., 2021; Chen et al., 2022). In this context, TMS has been also used as a tool useful to enhance understanding of the pathophysiological processes related to PD-induced tremor (Lefaucheur, 2005; Vucic et al., 2023). However, only when used in its "repetitive" mode (i.e. repetitive-TMS [r-TMS]) it can modulate brain functions through "plasticity" effects, in order to act directly on tremor-related neural networks, and also gaining potential therapeutic benefits (Lefaucheur et al., 2020). As a matter of fact, several studies reported short- and/or long-lasting beneficial effects using r-TMS on PD symptoms (such as tremor), both using excitatory and inhibitory protocols on different brain regions, such

*Abbreviations:* PD, Parkinson's Disease; DBS, Deep Brain Stimulation; TMS, Transcranial Magnetic Stimulation; r-TMS, Repetitive-TMS; TPS, Transcranial Pulse Stimulation; GABA, γ-aminobutyric acid; BDNF, Brain-derived neurotrophic factor; GDNF, Glial cell line-derived neurotrophic factor; VEGF, Vascular endothelial growth factor; MRI, Magnetic Resonance Imaging; EMG, Electromyography; NO, Nitric Oxide.

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as primary motor cortex, supplementary motor area, (pre)frontal cortex, and cerebellum (see, for example, Bologna et al., 2015; Chou et al., 2015; Chung and Mak, 2016; Le Faivre et al., 2016; Wagle Shukla et al., 2016; Goodwill et al., 2017; Yang et al., 2018; Frey et al., 2021; Lu et al., 2024; Wang et al., 2024).

However, advances in (non-invasive) brain stimulation techniques are constantly progressing. In this context, Transcranial Pulse Stimulation (TPS) is a novel, painless, and safe new technique which allows a mechanical effect, induced by shock waves. More specifically, although the exact underlying mechanisms have not yet been fully elucidated, TPS seems to act on mechano-sensitive ion channels: these mechanical stimuli are thus transduced into bio-chemical signals, triggering a cascade of responses (compare with Ingber, 2006; Fomenko et al., 2018; Zhang et al., 2021; Zhu et al., 2023), finally resulting in a likely and supra-threshold firing of stimulated neurons (see Weinreb and Moses, 2022). This process may lead to a change in brain neurotransmitters (in terms of concentrations) such as dopamine, serotonin, and γ-amino-butyric acid (GABA). Also, mechanisms related to growth factors and neurotrophins such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and vascular endothelial growth factor (VEGF) seem to be involved (see Min et al. 2011; Yang et al., 2012; Lin et al., 2015, Yahata et al., 2016; compare with Beisteiner et al., 2019; Cheung et al., 2023b). Accordingly, TPS has been recently proposed as a potential intervention for treating cognitive decline in patients with cognitive impairments: studies have reported a transitory improvement in cognitive performance in Alzheimer's Disease patients, by using different TPS protocols (see Beisteiner et al., 2019; Popescu et al., 2021; Cont et al., 2022; Matt et al., 2022a; Fernández-Castaño et al., 2023; Chen et al., 2024). In this context, TPS is suggested to result in effects on cortical activity that may be similar to those observed by using r-TMS protocols (Nardone et al., 2014; Beisteiner et al., 2019; Cont et al., 2022). Similarly, very recent data from a retrospective study seem to suggest a novel and possible improvement also for motor symptoms in Parkinson's Disease (Osou et al., 2023).

As a consequence, starting from this evidence (and basing on hypotheses suggesting the presence of neural hypo-activity in the motor cortex of PD patients as the result of a reduced thalamo-cortical governance), we here aim to investigate the possible effects induced by TPS (administered on motor regions) on PD-induced tremor of upper limbs, as a novel possibility for improving the management and rehabilitation of this neurodegenerative disease.

## 2. Materials and methods

### 2.1. Recruitment of participants

The eligibility criteria for participants were defined aiming to ensure a uniform sample, as in the following: I) age: 18 years or older; II) capability to provide written informed consent; III) meeting the MDS (International Parkinson and Movement Disorder Society) criteria for diagnosis of idiopathic Parkinson's Disease; IV) exhibiting a "tremor-dominant" PD phenotype, according to Poewe and Gerstenbrand (1986). Each participant underwent a brain Magnetic Resonance Imaging (MRI) scan before the TPS session (1.5 T, Philips, the Netherlands). Participants with structural abnormalities, tumors, recent brain trauma, and/or any other brain pathologies were excluded. Other main exclusion criteria were contraindications to TPS administration (e.g. thrombosis, cortisone treatments within 6 weeks before the first application, metal objects in the head, pacemakers, pregnancy, etc.). Every patient voluntarily agreed to take part to this intervention, and no compensation was provided for participating in this study. On this basis, 16 participants (age 52–83 years; 5 females) were initially enrolled as eligible for participating in TPS procedures. Of these, 9 patients (age 52–77 years; 3 females) were involved in sham-controlled, as described in the following. Patients were always treated and evaluated in pharmacologically "ON" state. All methods were conducted in accordance with Institutional Review Board and followed the ethical principles outlined in the Declaration of Helsinki. Participants provided a written and informed consent before taking part in the procedures. They were allowed to retire in every moment with no consequences on their routine medical assistance.

### 2.2. Clinical, demographic, and experimental data collection

Clinical and demographic data were collected, considering indices such as age, gender, disease duration, most affected side, presence of additional therapies, levodopa administration and equivalent daily doses. In addition, clinical evaluations of motor impairment such as UPDRS-III score (and sub-scores specifically related to tremor) were gathered for each patient (comparing baseline [T0] with measurements obtained after the end of the treatment [T1] and 24 h after TPS [T2]; scale from 0 to 132, and from 0 to 40, respectively).

When considering evaluation of PD-induced resting tremor, we recorded patient's tremor using a manual accelerometer, connected to an electromyography (EMG) system (Natus Synergy, Synopo, Italy), to evaluate amplitude and frequency of oscillations. Thus, for each patient, accelerometer signal recordings were obtained at baseline (T0; i.e. before TPS intervention), immediately after TPS session (T1), and 24 h post-TPS (T2). At the end of the study, each patient was also asked to fill out a VAS scale (0–10, ranging from "no improvement" [i.e. 0] to "total/maximal improvement/resolution" [i.e. 10]) about possible and subjective amelioration of indices such as tremor, rigidity, and bradykinesia in the 24 h after the TPS session (T2; in comparison to pre-treatment, T0).

### 2.3. TPS protocol

When considering the stimulation protocol, the Neurolith© TPS Transcranial Pulse Stimulation device (Storz Medical AG, Tägerwilen, Switzerland) was used. This system allows a confident neuronavigation using individual 3D T1 isometric voxel MRI scans. The treatment protocol was defined with TPS delivery set at 4 Hz and 0.20mJ/mm$^2$. A single-session of 1500 pulses was administered to the participants' motor cortex, contralateral to the body side that was more affected by the resting tremor (i.e. if tremor was mostly evident on the right hand, TPS was applied on the left motor cortex). The session was divided in 3 rounds of 500 pulses each, with pauses of 5 min between blocks. At the end, all participants received 30 min TPS sessions. As anticipated, in 9 participants a sham-session was also performed in a separate day (wash-out period among sessions of at least 30 days), using the same criteria as the regular session but applying a separator to the TPS coil (i.e. an empty plastic thickness of about 3 cm) in order to avoid cortex stimulation.

### 2.4. Statistics

Due to the novelty of the here reported approach in PD-induced tremor, data were analyzed considering "exploratory" statistics. More specifically, all raw data (i.e. accelerometer recordings of the resting tremor [amplitude, expressed in μV; frequency, expressed in Hz]; UPDRS-III scores [expressed on a scale ranging from 0 to 132; higher symptoms severity corresponding to higher score values; sub-scores related to tremor ranging from 0 to 40], and qualitative improvement scores [expressed on a scale ranging from 0 to 10; higher improvements corresponding to higher values]) were evaluated for normality distribution (Shapiro-Wilk Test). Successively, all main factors (i.e. time of evaluation −baseline [T0], post-session [T1], and 24 h from the end of the session [T2]-, and, for a subsample of 9 participants, stimulation condition −TPS vs. sham-) and their possible interactions were considered as paired "within-group" comparisons by using Student's *t*-test (in normally distributed data) or Wilcoxon signed-rank test (in not normally distributed data). An estimation/approximation of effect sizes (please refer to Lehnard & Lehnard, 2022) for significant data was also reported

by means of *Cohen's d* (absolute values; $0.2 < d < 0.5$ = *small effect*; $0.5 < d < 0.8$ = *medium effect*; $d > 0.8$ = *large effect*), in order to better describe the possible "real" size of reported effects.

A correlation analysis was also performed (Pearson correlation −normally distributed data- or Gamma statistic −not normally distributed data with ties-) considering clinical, demographic, and experimental data. Significance was always set at $p < 0.05$ (two-tailed).

## 3. Results

### 3.1. Clinical and demographic description of the experimental sample

Clinical and demographic characteristics of the experimental sample (i.e. age, gender, disease duration, most affected side, levodopa administration and equivalent daily doses, presence of additional therapies) are reported in Table 1. No significant side effects were reported by participants after TPS administration.

### 3.2. Accelerometer data

When considering the total sample of 16 participants, accelerometer data (amplitudes of resting tremor) resulted in significant differences when comparing post-session evaluations with baseline recordings (T1: $p = 0.002$; *Cohen's d* = 0.933, *large effect size*; T2: $p < 0.001$; *Cohen's d* = 1.168, *large effect size*). Accelerometer data also resulted in significant differences when comparing TPS vs. sham (9 participants). More specifically, effects were evident immediately after the end of the intervention (T1: $p = 0.004$; *Cohen's d* = 1.341, *large effect size*; no differences in baseline values [T0: $p = 0.57$]), suggesting that TPS was more effective than placebo in improving resting tremor in PD patients. In this context, a significant improvement was evident in the TPS group when considering baseline (i.e. pre-intervention, T0), post-session values (T1: $p = 0.039$; *Cohen's d* = 0.889, *large effect size),* and recordings obtained 24 h after the end of the intervention (T2: $p = 0.004$; *Cohen's d* = 0.837, *large effect size*). On the other hand, sham resulted in significant improvement only when considering baseline and recordings obtained 24 h after the end of intervention (T2: $p = 0.032$; *Cohen's d* = 1.002, *large effect size*). Thus, these findings indicate that TPS may be able to improve resting tremor in PD more effectively than placebo, especially in the immediate period after session completion. Data are reported in Table 2 and Fig. 1. No significant differences were evident when considering frequency of the resting tremor, that always oscillated around 9–10 Hz in every condition.

### 3.3. UPDRS-III

When considering the total sample of 16 participants UPDRS-III showed significant differences when comparing post-session evaluations with baseline recordings (T1: $p = 0.027$; *Cohen's d* = 2.962, *large effect size*; T2: $p < 0.001$; *Cohen's d* = 2.754, *large effect size*), as well as when post-session time points were compared each other ($p < 0.001$; *Cohen's d* = 2.602, *large effect size*). Similar findings were evident in subscale values related to tremor when compared to baseline recordings (T1: $p = 0.003$; *Cohen's d* = 1.491, *large effect size*; T2: $p = 0.002$; *Cohen's d* = 1.262, *large effect size*).

When considering TPS vs. sham (no differences in baseline values between conditions; T0: $p = 0.19$), TPS resulted in a more consistent effect when considering evaluations obtained after 24 h from the end of the intervention (T2). More specifically, a significant difference was obtained with respect to baseline evaluation (T0: $p = 0.005$; *Cohen's d* = 2.673, *large effect size*), and with respect to recordings obtained immediately after session completion (T1: $p = 0.004$; *Cohen's d* = 3.263, *large effect size*). Data are reported in Table 2 and in Fig. 2. When considering values obtained from specific sub-scales related to tremor, significant findings were evident in the TPS condition when comparing baseline evaluation and data obtained 24 h after the end of the intervention (T2: $p = 0.002$; *Cohen's d* = 4.157, *large effect size*). However, in this case, also sham resulted in significant differences when comparing post-treatment evaluations with baseline recordings (T1: $p = 0.028$; *Cohen's d* = 3.562, *large effect size*; T2: $p = 0.04$; *Cohen's d* = 2.483, *large effect size*). Comparison of TPS and sham resulted in a trend toward significance suggesting higher improvements in the TPS group after 24 h from the end of the treatment (T2: $p = 0.095$; *Cohen's d* = 1.039, *large effect size*; data are reported in Table 2). Thus, TPS may be useful for improving motor symptoms and tremor-related outcomes in PD patients. No other significant changes were evident in the remaining comparisons.

### 3.4. Qualitative evaluation of (motor) improvement

A qualitative/subjective evaluation of possible (motor) improvements experienced by participants was also performed by considering indices such as tremor, rigidity, and bradykinesia (comparing possible improvements after 24 h from the end of the treatment [T2] with respect to baseline/pre-treatment [T0]).

When considering the total sample of 16 participants, qualitative improvements were always significant (with respect to 0 −i.e "no improvement"-; tremor: $p < 0.001$; *Cohen's d* = 1.718, *large effect size;* rigidity: $p = 0.016$; *Cohen's d* = 0.671, *medium effect size*; bradykinesia:

**Table 1**
Clinical and demographic characteristics of the experimental sample. Participants marked with * were also involved in sham procedures.

| Participants/ Indices | Age (years) | Disease Duration (years) | Most Affected Side | Levodopa (mg) | Additional Therapies | Levodopa Equivalent Daily Dose (mg) |
|---|---|---|---|---|---|---|
| **A *(male)*** * | 74 | 3 | R | 400 | Yes (MAO-B) | 500 |
| **B *(male)*** * | 65 | 14 | R | 350 | Yes (MAO-B) | 600 |
| **C *(male)*** * | 75 | 2 | L | 400 | No | 400 |
| **D *(male)*** * | 70 | 2 | L | 300 | Yes (MAO-B) | 350 |
| **E *(female)*** * | 73 | 4 | L | 300 | Yes (Dopamine Agonists) | 420 |
| **F *(male)*** * | 52 | 6 | L | 300 | Yes (Dopamine Agonists) | 600 |
| **G *(male)*** * | 63 | 1 | R | 300 | Yes (MAO-B) | 400 |
| **H *(female)*** * | 72 | 7 | L | 475 | Yes (COMT Inhibitors) | 712.5 |
| **I *(female)*** * | 77 | 7 | L | 550 | Yes (Muscarinic Blockers) | 800 |
| **J *(female)*** | 72 | 9 | R | 350 | Yes (COMT Inhibitors) | 525 |
| **K *(male)*** | 73 | 8 | R | 1000 | Yes (MAO-B; COMT Inhibitors; Muscarinic Blockers) | 1750 |
| **L *(male)*** | 63 | 8 | L | 400 | Yes (Dopamine Agonists) | 550 |
| **M *(female)*** | 78 | 22 | L | 500 | Yes (Dopamine Agonists; MAO-B Inhibitors) | 790 |
| **N *(male)*** | 77 | 12 | R | 800 | Yes (Dopamine Agonists; MAO-B Inhibitors) | 1060 |
| **O *(male)*** | 83 | 10 | R | 400 | Yes (MAO-B) | 500 |
| **P *(male)*** | 65 | 3 | R | 400 | No | 400 |

**Table 2**
Summary of values obtained in the various indices that have been considered.

| | TPS (16 participants) | | |
|---|---|---|---|
| *Indices/Conditions* | ***Baseline*** | ***Post-Intervention*** | ***24 h Post-Intervention*** |
| ***Accelerometer (expressed in μV)*** | 615.2 (± 521.0) | 343.2 (± 307.0) | 347.8 (± 343.2) |
| ***UPDRS-III (scale from 0 to 132)*** | 28.8 (± 14.6) | 26.9 (± 13.9) | 22.6 (± 13.6) |
| ***UPDRS-III (tremor sub-scale from 0 to 40)*** | 9.6 (± 3.9) | 7.5 (± 3.9) | 6.9 (± 3.6) |
| | ***Tremor*** | ***Rigidity*** | ***Bradykinesia*** |
| ***Tremor (qualitative improvement; scale from 0 to 10)*** | 4.4 (± 2.5) | 1.9 (± 2.7) | 1.6 (± 2.3) |

| | real TPS (9 participants) | | | Sham (9 participants) | | |
|---|---|---|---|---|---|---|
| *Indices/Conditions* | **Baseline** | **Post-Intervention** | **24 h Post-Intervention** | **Baseline** | **Post-Intervention** | **24 h Post-Intervention** |
| ***Accelerometer (expressed in μV)*** | 621.9 (± 518.7) | 281.8 (± 195.1) | 327.0 (± 258.9) | 673.0 (± 344.1) | 513.7 (± 169.9) | 441.1 (± 191.5) |
| ***UPDRS-III (scale from 0 to 132)*** | 24.4 (± 9.6) | 23.4 (± 8.9) | 18.7 (± 7.7) | 24.7 (± 14.6) | 24.1 (± 14.6) | 22.3 (± 15.0) |
| ***UPDRS-III (tremor sub-scale from 0 to 40)*** | 8.1 (± 3.6) | 7.0 (± 4.5) | 6.2 (± 3.2) | 9.0 (± 4.4) | 8.0 (± 4.2) | 7.9 (± 4.5) |
| | **Tremor** | **Rigidity** | **Bradykinesia** | **Tremor** | **Rigidity** | **Bradykinesia** |
| ***Tremor (qualitative improvement; scale from 0 to 10)*** | 4.3 (± 2.5) | 1.1 (± 1.8) | 1.3 (± 2.0) | 3.3 (± 2.6) | 0.0 (± 0.0) | 0.1 (± 0.3) |

Data are reported as means ± standard deviations. Qualitative improvement has been evaluated 24 h after the end of the intervention.

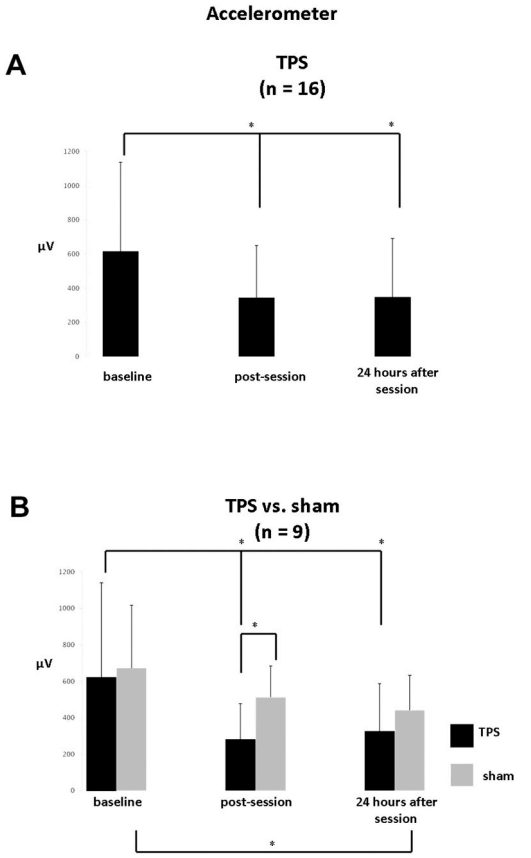


**Fig. 1. Representation of findings obtained when considering accelerometer data.** A.Representation of accelerometer data for the entire sample of participants (TPS). B.Representation of accelerometer data for TPS vs. sham. Significant comparisons are reported by means of an asterisk (*).

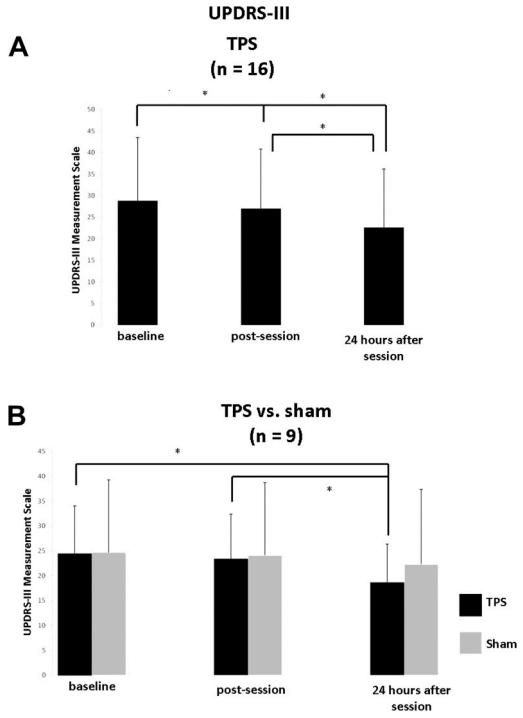


**Fig. 2. Representation of findings obtained when considering UPDRS-III data.** A.Representation of UPDRS-III data for the entire sample of participants (TPS). B.Representation of UPDRS-III data for TPS vs. sham. Significant comparisons are reported by means of an asterisk (*).

p = 0.031; *Cohen's d* = 0.681, *medium effect size*). On the other hand, no significant findings were evident when considering TPS vs. sham. Data are reported in Table 2.

### 3.5. Correlation analysis

In the correlation analysis, aside from the "expected" correlations (e.g. positive correlations among recorded indices, symptom severity, pharmacological doses, disease duration, etc. –statistics not reported-), we observed a significant positive correlation between qualitative/subjective improvement in rigidity and the use of dopamine agonists (in addition to levodopa; Gamma statistic = 0.78) in the total sample of participants (n = 16) who underwent TPS.

## 4. Discussion

As one of the first studies in the field of TPS administration in PD, present findings suggest that, when applied on motor regions, TPS may be more effective than sham (i.e. placebo) in (transiently) improving motor symptoms such as resting tremor in PD patients, with evidence

that may develop over time after the end of the treatment. In agreement with previous r-TMS protocols (Yang et al., 2018; Frey et al., 2021), TPS produced a reduction in motor signs such as the amplitude of tremor (but not in its frequency). Importantly, tremor reduction was followed by a clinical improvement in motor impairment, as measured by UPDRS-III (and corresponding sub-scores specifically related to tremor), and lasting at least 24 h after TPS intervention.

### 4.1. TPS as a novel solution for neuromodulation

Recently, techniques that are akin to shock waves such as the application of ultrasound stimulation (both centrally and peripherally) have become a "hot topic" in the field of neuroscience and neuromodulation, as they bear the potential for providing a new class of non-invasive stimulation (e.g. Manganotti and Amelio, 2005; Amelio and Manganotti, 2010; Manganotti et al., 2012; Santamato et al., 2013, 2014; Zhang et al., 2021; Chen et al., 2024). In this context, TPS is a novel method for non-invasive brain stimulation, that exploits short and single pulses of mechanical waves, called "shock-waves". The immediate result of these waves is the generation of pulses, each lasting about 1 μs. In contrast to "common"/"classical" ultrasound, this pulse is followed by a tensile wave with a mitigating effect useful for reducing amplitude, which lasts for about 4–5 μs. Besides being highly focal, "shock-waves" are likely not restricted to superficial layers of the brain only: as a matter of fact, TPS is reported to stimulate up to 8 cm in depth, as tested for its practicability with mice, human skulls, and brain specimens (compare with Beisteiner et al., 2019; Cheung et al., 2023b). Crucially, TPS operate with safe margins, with no relevant adverse events normally reported in human studies (Radjenovic et al., 2022). However, while the main mechanisms of the peripheral effects of ultrasound stimulation are quite well known (and usually resulting in increased metabolism, angiogenesis, and anti-inflammatory effects in relation to Nitric Oxide [NO] release in the stimulated tissues; see, for example, Mariotto et al., 2005), the same is still not clearly defined for TPS. In this context, considering that TPS seems to act on mechano-sensitive ion channels (possibly resulting in a supra-threshold firing of stimulated neurons; compare with Ingber, 2006; Fomenko et al., 2018; Zhang et al., 2021; Weinreb and Moses, 2022; Zhu et al., 2023), it can be suggested that similar mechanisms would be evident when ultrasounds are applied to the Central Nervous System, with possible increase of metabolism in the stimulated brain regions due to the release of NO or effects on membrane permeability (compare with Hatanaka et al., 2016; Eguchi et al., 2018; Beisteiner et al., 2019; Meng et al., 2021). Moreover, processes related to changes in brain neurotransmitters (such as dopamine, serotonin, and GABA) and mechanisms related to BDNF, GDNF, and VEGF are suggested to be involved (see Min et al. 2011; Yang et al., 2012; Lin et al., 2015, Yahata et al., 2016; compare with Beisteiner et al., 2019; Cheung et al., 2023b).

### 4.2. TPS in PD and neurodegenerative diseases

Compatibly, pivotal studies reported clinical effects of ultrasound techniques or TPS administration on different types of patients, ranging from effects on arousal in Minimal Conscious State Syndrome after brain injury (e.g. Lohse-Busch et al., 2014; Monti et al., 2016) to improvements in memory and/or cognitive performance in Alzheimer's Disease and in patients affected by mild/moderate cognitive impairments (Beisteiner et al., 2019; Popescu et al., 2021; Cont et al., 2022; Dörl et al., 2022; Fernández-Castaño et al., 2023; Fong et al., 2023; Chen et al., 2024). Also, TPS has been recently investigated for the treatment of Depression, Attention Deficit Hyperactive Disorder, and Autism Spectrum Disorder (see Cheung et al., 2022a, 2022b, 2023a, 2023b, 2023c; Matt et al., 2022a). Interestingly, after repeated sessions of TPS, improvements have the potential to be significant, persistent, and long-lasting (see Matt et al., 2022b). In the end, combining all the reported evidence, the possible mechanisms of TPS could favour an increase in the metabolism of the stimulated brain regions, helping to explain the positive clinical effects observed on these disturbances.

In the context of PD, TPS is a novel application and it could be still difficult to hypothesize/verify its neural mechanisms. In fact, at the best of our knowledge, only a case-series abstract (Lohse-Busch, 2022) and a retrospective (not sham controlled) study are available (Osou et al., 2023), mainly suggesting the presence of clinical improvements in motor behaviour and with no major adverse effects (also a completed trial with no posted results has been individuated; https://clinicaltrials.gov/study/NCT04333511). Compatibly with the present work, these studies report a clear improvement in motor symptoms of PD participants, as measured by means of the UPDRS scale. In this context, when considering clinical evidence, previous brain stimulation studies showed that motor symptoms such as tremor may be very sensitive to neuromodulation, as suggested by the utilization of DBS on drug-resistant PD patients (Bronstein et al., 2011; Oswal et al., 2016). Compatibly, DBS is mainly suggested to induce a marked reduction of fast brain frequencies (i.e. beta) as recorded at the sub-thalamic nucleus, thus resulting in motor improvements (Oswal et al., 2016). As to better understanding tremor pathophysiology (compare with Deuschl et al., 2001; Deuschl and Bergman, 2002; Helmich et al., 2013; Dirkx et al., 2017; van der Stouwe et al., 2020; Dirkx and Bologna, 2022), also non-invasive TMS has been used and investigated. As already mentioned, r-TMS displayed short- and/or long-lasting effects on PD symptoms, both using excitatory and inhibitory protocols. This has been obtained by modulating the primary motor cortex or other brain regions such as the supplementary motor area, the (pre)frontal cortex, and/or the cerebellum (compare with Bologna et al., 2015; Chou et al., 2015; Chung and Mak, 2016; Lefaivre et al., 2016; Wagle Shukla et al., 2016; Goodwill et al., 2017; Yang et al., 2018; Frey et al., 2021; Lu et al., 2024; Wang et al., 2024). Again, evidence suggests a potential benefit when acting on impaired neural networks, thus modulating brain functions through the possible induction of neural plasticity (e.g. acting on oscillations of the cortico-basal-thalamo-cortical and/or cerebello-thalamo-cortical circuits, thus modulating/improving neural activity in motor regions). In conclusion, basing on this evidence and on possible TPS mechanisms (see section 4.1), we can here suggest a possible "modulatory" and/or "excitatory" effect of TPS that may favour an increased metabolism of the (extended) motor circuits of PD participants, thus resulting in a clinical decrease of tremor.

## 5. Conclusions

In conclusion, the present study is a novel, explorative, pivotal, sham-controlled investigation of the possible effects of TPS in PD. Surely, possible limitations such as the small sample size or evaluations done in "ON" mode only will have to be overcome in the next future. However, basing on present findings it can be stated that: I) TPS on motor cortex transitorily improves the resting tremor in the contralateral upper limb of PD patients; II) TPS shows positive short-term effects at a clinical level, as assessed by UPDRS-III and supported by subjective feedback; III) TPS was generally well tolerated and showed no side effects; IV) interaction between TPS and pharmacological intervention should be explored in a deeper way (see correlation findings). Thus, future studies are mandatory to further understand therapeutic effects of TPS as a possible and effective "add-on" intervention in the management of PD, as well as possible other applications of this technique on other (motor) disorders.

## 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. **Mauro Catalan:** Writing – review & editing, Conceptualization. **Pierpaolo Busan:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Formal analysis.

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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.

## Data availability

Data will be made available on request.

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