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Additional Declarations: Yes there is potential Competing Interest. F.O.B. and F.G. are named inventors on a USA patent (National Phase in U.S. No. 17/926278, Title “Control method for a neuroprosthetic device for the reduction of pathological tremors”) based on International Application PCT/EP2021/063189, which describes a method for controlling a neuroprosthetic device for the treatment of tremor, in particular ET and PD, by intramuscular stimulation of muscle spindles. F.O.B., C.M.P., A.P.V., F.G. and J.R.P.S. are named inventors on a request for grant of a European patent (submission number 300571696, application number EP25382795.0) that describes a system for monitoring and reducing pathological tremor in a user.

Tremor reduction and modulation of thalamic and spinal activity with closed-loop peripheral electrical stimulation

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Abstract

Essential tremor (ET), a disorder driven by abnormal neural oscillatory activity, affects approximately 25 million people worldwide and substantially impairs daily activities and quality of life. Here, we identify neurophysiological mechanisms underlying tremor suppression induced by customized, closed-loop sensory peripheral electrical stimulation (PES). Fourteen patients with medication-refractory ET received PES synchronized to tremor activity or sham stimulation. Active PES reduced tremor and was associated with decreased disynaptic group I inhibition between wrist flexor and extensor muscles, alongside reduced oscillatory power of local field potentials recorded from the ventral intermediate nucleus of the thalamus. These effects were significantly attenuated during sham stimulation. A single 20-minute PES session reduced tremor severity by 30.00%, compared to 7.70% after sham. Daily treatment over two weeks produced progressive benefits, with tremor reduction reaching 40.51% from the first to the final day. These findings show that phase-locked PES provides effective, noninvasive tremor suppression without adverse effects, potentially associated with modulation of segmental spinal circuits and central oscillatory dynamics. This approach could offer a practical alternative or complement to current therapies.

Pathological tremor usually manifests as a roughly rhythmic involuntary oscillation of a body part and can arise from various neurological conditions, including essential tremor (ET), Parkinson's disease (PD), and dystonia [1]. Aberrant neural oscillatory activity is a common hallmark of these conditions, particularly in ET, one of the most prevalent movement disorders worldwide [2]. In

recent years, ET has been increasingly recognized as a complex disorder that is both etiologically and clinically heterogeneous [1]. ET severely hampers the execution of simple daily tasks, such as drinking, writing, or typing, with over 90% of patients seeking medical attention reporting functional disability [3]. In severe cases, individuals cannot feed or dress independently [4], often leading to reduced work capacity or forced early retirement. Affecting an estimated 25 million people worldwide [2], ET imposes a significant economic burden, with direct medical costs in the U.S. alone reaching $9.4 billion annually [5].

Despite its high prevalence and significant impact on daily life, current ET treatments remain limited. As the underlying pathophysiology of the disease remains incompletely understood, pharmacotherapy is often nonspecific and only partially effective. Although medication remains the first-line treatment for ET, its efficacy is often limited. Moreover, adverse effects such as sedation, nausea, ataxia, fatigue, and impaired concentration can limit tolerability and hinder optimal treatment outcomes [6]. Consequently, nearly one-third of ET patients prescribed tremor medication cease treatment [7]. Disabling, drug-resistant tremors can be addressed with second-line approaches that involve surgery, such as deep brain stimulation (DBS) or magnetic resonance-guided high-intensity focused ultrasound (HIFU). While these interventions can achieve significant tremor reduction (23-87% improvement for DBS [8]; 12.2-66% improvement for HIFU [9]), many patients are not suitable candidates. Older adults (for DBS), individuals on anticoagulant therapy (relative contraindication), and patients hesitant to undergo invasive or ablative brain procedures frequently decline or are excluded from surgical interventions. Furthermore, the high cost of these procedures often plays a decisive role. Consequently, the utilization of these invasive approaches is still residual: estimates from a major clinical center indicate that only 2.90% of ET patients and 1.38% of PD patients undergo DBS surgery [10]. Consequently, there is a growing unmet need for safe, effective, and noninvasive alternatives that can be deployed broadly, especially for patients who are not candidates for or do not wish to pursue neurosurgical procedures.

Noninvasive neuromodulation has emerged as a promising therapeutic approach for tremor. Within this area, sensory peripheral electrical stimulation (PES) can modulate sensorimotor function through pulses delivered below the motor threshold (MT). By selectively recruiting afferent pathways without directly evoking muscle contractions, sensory PES alters afferent input to spinal and supraspinal circuits, ultimately reshaping excitability and coupling within the tremor network. This rationale is especially compelling in ET, where tremor generation is thought to depend on aberrant oscillatory activity and altered interactions among network nodes spanning the cerebello-thalamo-cortical loop and down into spinal motor pools [11] [12]. However, the current evidence supporting the application of sensory PES in tremor is limited by key methodological constraints. Relatively few studies have incorporated rigorous sham-controlled designs, despite the natural variability of tremor and its susceptibility to placebo effects. On the other hand, although some reports have shown clinical and/or kinematic improvements [13] [14] [15], mechanistic links to the underlying neurophysiology are not deeply explored. Progress toward personalized and optimized stimulation protocols requires identifying measurable physiological markers that vary alongside symptom improvement.

Two mechanistic levels are particularly relevant for evaluating how sensory PES may reduce tremor. First, at the spinal level, tremor severity may be influenced by inhibitory interactions that shape agonist-antagonist coordination [16]. Disynaptic group I inhibition is a candidate mechanism because it regulates inhibitory pathways between antagonist muscles, potentially limiting the emergence or amplification of rhythmic co-activation patterns. Second, tremor expression in ET is associated with central oscillatory activity within the cerebello-thalamo-cortical network, with the ventral intermediate nucleus (VIM) of the thalamus serving as a key node [17] [18].

Here, we tested the hypothesis that closed-loop sensory PES, delivered in synchrony with tremor activity, engages afferent pathways to modulate neural circuits involved in tremor generation and propagation in ET. We used a crossover, sham-controlled design to quantify short-term effects of PES on tremor and investigate its underlying neurophysiological mechanisms. First, we examined whether tremor suppression was associated with changes in disynaptic group I inhibition between wrist flexor and extensor muscles, linking clinical

effects to modulation of spinal inhibitory circuitry. Second, to assess potential effects on supraspinal circuitry, we analyzed intracranial recordings from a subset of patients with implanted DBS systems and quantified changes in the oscillatory power of local field potentials (LFPs) recorded from the VIM of the thalamus. Finally, we hypothesized that repeated daily application of PES would produce cumulative and longer-lasting therapeutic effects. To test this, we evaluated the clinical relevance of repeated stimulation over a two-week personalized PES regimen using longitudinal clinical and kinematic assessments.

Results

To evaluate the short-term efficacy of customized, phase-locked sensory PES (closed-loop), we conducted a sham-controlled study involving 14 patients with medication-refractory ET. Each participant completed two experimental sessions: one consisting of 20 minutes of active PES (divided into 20 trials of 1 minute each) and another involving sham stimulation. The order of the sessions was randomized to minimize potential bias, and a minimum interval of 48 hours was maintained between sessions to mitigate any carry-over effects. A schematic overview of the experimental protocol is presented in Fig. 1a. Additionally, a subset of 12 patients participated in a separate longitudinal study investigating the long-term effects of two consecutive weeks of active PES.

Electrical stimulation was applied bilaterally using surface electrodes. These were placed over the cubital fossa and the radial groove to selectively target the median and radial nerves, respectively, while a common anode was positioned over the olecranon (see Fig. 1b). Muscle activity was monitored via bipolar surface electromyography (sEMG) recordings from the flexor carpi radialis (FCR) and extensor carpi radialis (ECR) muscles. PES consisted of biphasic pulses at 100 Hz with a pulse width of 400 μs (see Fig. 1b and Fig. 2), delivered through a custom system combining an sEMG amplifier and a voltage-controlled stimulator.

At the beginning of both active and sham sessions, MTs (defined as the minimum amount of current that elicited a motor response) were individually determined for each arm and muscle. During active PES, intensity was set just below the MT, whereas in sham trials, it was set to zero. PES was delivered following a validated closed-loop control method (selective and adaptive timely stimulation - SATS) [15], which alternates between EMG recording and stimulation periods to prevent signal artifacts due to electrical stimulation. Specifically, SATS was delivered with an out-of-phase approach (i.e., stimulation of the antagonist muscle of the one generating tremorgenic movements), guided by real-time sEMG. This approach targets Ia afferent fibers to reduce disynaptic group I inhibition. During each 1-min trial, participants maintained upper limb postures that elicited tremor (e.g., keeping the arms extended, flexing the elbows, holding two paper cups to the mouth (see Fig. 1b)). Rest periods were provided between trials as needed.

Short-term suppression of tremor

Clinical and kinematic assessments were performed at both the beginning (PRE) and the end (POST) of each session. The clinical evaluation included the Fahn-Tolosa-Marin (FTM) tremor rating scale (covering the severity, motor tasks, and functional disability subscales), as well as the clinical global impression (CGI) of severity. At the end of each active or sham session, the FTM severity and motor tasks subscales were reassessed together with the CGI of change. For the kinematic assessment, 11 wireless inertial measurement units (IMUs) were attached to each participant at the following locations (see Fig. 1b): head, sternum, pelvis, both shoulders, both upper arms, both forearms, and both hands. IMU data were collected and transmitted wirelessly while participants performed the assessment tasks before and after the stimulation trials. Raw IMU data were analyzed offline to extract acceleration signals from the embedded sensors. We focused primarily on the acceleration modulus from the hand-mounted IMUs, as the hand represents the distal segment most severely affected by tremor [19] and the main therapeutic target. The root mean square (RMS) of this acceleration modulus was calculated to serve as a comprehensive metric of overall hand motion. This metric was normalized to pre-intervention values and expressed as a percentage of the baseline for both the most affected and the least affected sides.

The severity subscale of FTM showed that active stimulation produced a significant reduction of tremor from PRE stimulation to POST

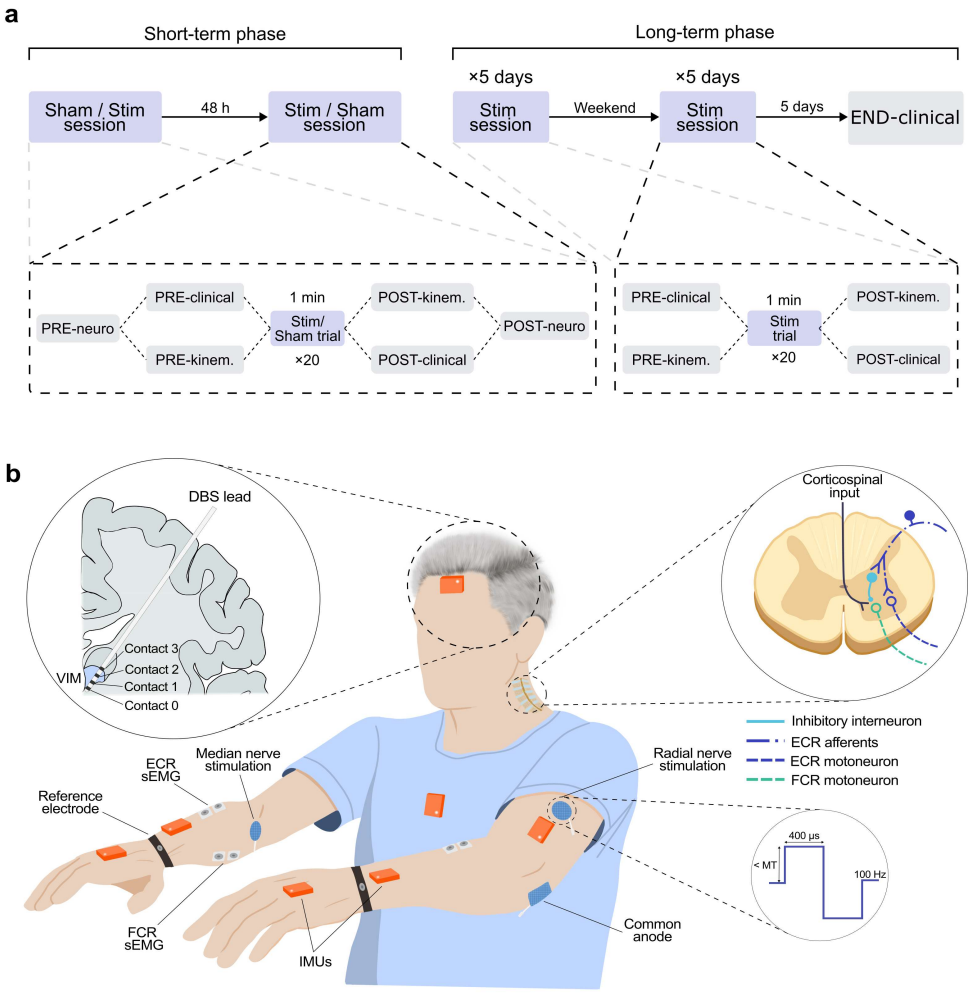


Fig. 1 Overview of the experimental design and procedures. a Schematics of the experimental sessions. Patients with ET participated in two separate phases of the study, as detailed in Supp. Table 1: one where the short-term effects (before and right after peripheral electrical stimulation (PES) therapy) were evaluated and another one where the effects of PES were assessed for two consecutive weeks (long-term). In the short-term phase, clinical scales ('clinical'), kinematic ('kinem.') and neurophysiological ('neuro') metrics were assessed before and after 20 minutes of active ('Stim') or 'Sham' stimulation. Long-term sessions included clinical scales and kinematic assessments before and after 20 minutes of active stimulation, with an additional evaluation conducted five days after the final stimulation session. **b** Full experimental setup showing IMU location (pelvis and shoulder IMUs are not shown) and electrodes placement to deliver PES therapy. PES therapy required recording EMG signals from flexor carpi radialis (FCR) and extensor carpi radialis (ECR) to drive the closed-loop stimulation of the median and radial nerves. (Top left inset) Intracerebral local field potentials (LFPs) recordings (from two patients with deep brain stimulation (DBS) devices implanted) were recorded before, during and after the short-term phase of the study. Contact points are labelled 0 to 3 (being 0 the most distal and 3 the most proximal with respect to the DBS lead). *BrainSense™ Survey* uses bipolar recordings, which are taken from 2 electrodes on the same lead. In our study, LFPs were recorded in both patients from contact pairs 0–3, 1–3, and 0–2. (Top right inset) Schematic representation of disynaptic group I inhibition circuit (inhibition from ECR to FCR).

stimulation, reaching 70.0 ± 21.4% (mean ± standard deviation) of baseline values (one-sample t-test, $p < 0.001$) (see Fig. 3a). In contrast, scores following sham stimulation remained close to baseline levels (92.3 ± 21.4% of PRE) and did not show a significant change (Wilcoxon signed-rank test, $p = 0.18$). Similar results were observed for the motor tasks subscale of FTM (see Fig. 3b), where active stimulation resulted in a significant decrease to 74.3 ± 17.4% of PRE stimulation values (one-sample t-test, $p < 0.001$). Fig. 3d illustrates representative spiral and line drawings from the

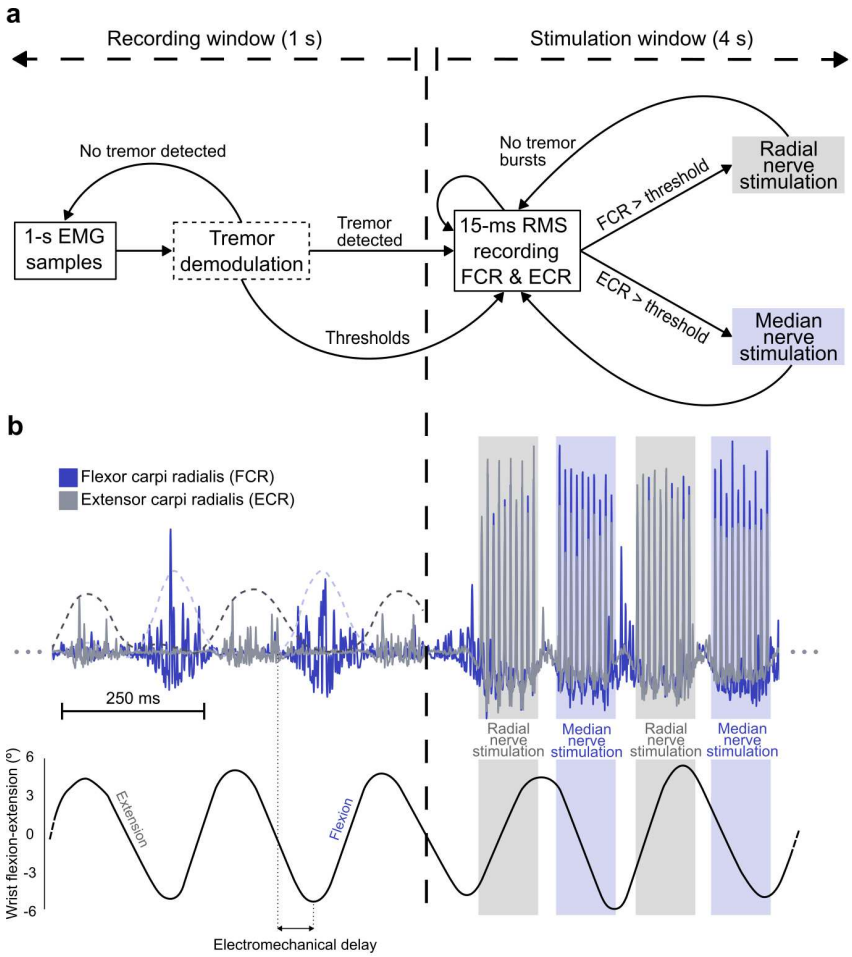


Fig. 2 Control flow diagram of the SATS strategy. a Control flow diagram of the selective and adaptive timely stimulation (SATS) strategy applied in this study. SATS consists of sequential recording and stimulation windows to minimize contamination of EMG signals by stimulation artifacts. **b** Representative example of EMG signals and wrist flexion-extension angle while the SATS strategy is applied to a pair of muscles (FCR and ECR) presenting tremor, illustrating the electromechanical delay between muscle activation and joint motion. SATS was delivered with an out-of-phase approach (*i.e.*, stimulation of the antagonist muscle of the one generating tremorgenic movements). Stimulation artifacts are visible in the EMG traces inside the stimulation window.

FTM motor tasks subscale, demonstrating marked post-stimulation improvement on the most affected side. Sham stimulation also led to a reduction, reaching 87.3 ± 15.3% of PRE, which was statistically significant (Wilcoxon signed-rank test, $p = 0.01$), although the magnitude of improvement was smaller than that observed with active stimulation. Overall, these findings indicate that active stimulation induced significantly greater relative reductions than sham in both the severity subscale (Wilcoxon signed-rank test, $p = 0.002$) and the motor tasks subscale (Wilcoxon signed-rank test, $p = 0.004$). Consistent with these results, the median CGI-Change score among the 14 patients was 2.5 in the active stimulation condition, corresponding to an improvement between 'Much improved' and 'Minimally improved'. By comparison, the median score in the sham condition was 4, indicating 'No change'. This further supports a greater perceived benefit following active stimulation than sham (Wilcoxon signed-rank test, $p = 0.01$).

Fig. 3c summarizes the median and interquartile range (Q1–Q3) of the normalized RMS of the hand acceleration modulus, for both the most and least affected sides, under sham and stimulation conditions. The most affected side showed median normalized values of 91.5 [70.5–101.5]% (median [Q1–Q3] % of PRE) during sham and

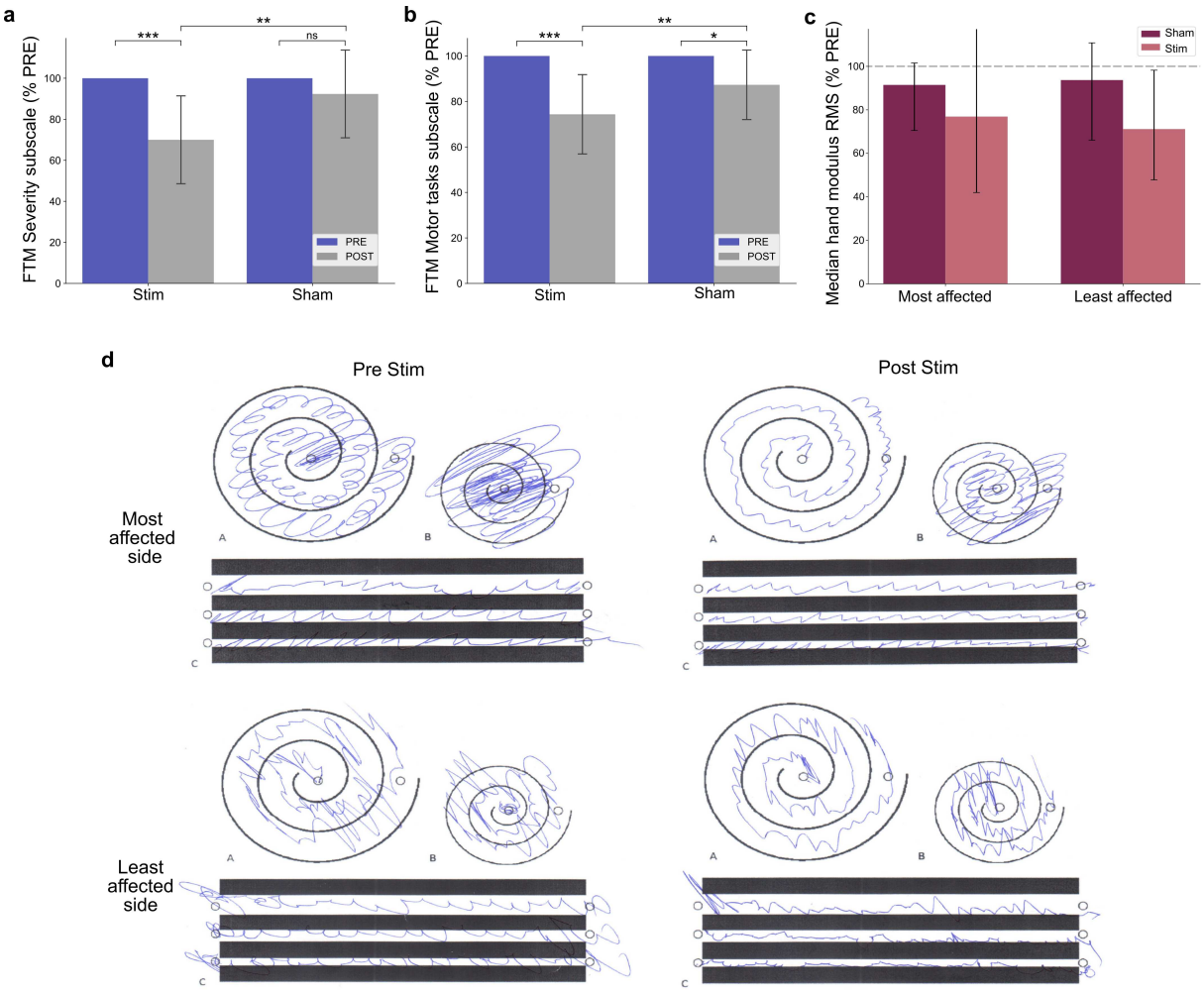


Fig. 3 Short-term results from clinical (**a**, **b**, **d**) and kinematic (**c**) assessments. **a** Fahn-Tolosa-Marin (FTM) severity subscale for sham and stimulation conditions (mean ± standard deviation). **b** FTM motor tasks subscale for sham and stimulation conditions. **c** Median hand modulus RMS. Error bars represent the interquartile range (Q1–Q3). For the most affected side, under the stim condition, the upper error bar extends beyond the top of the plot. **d** Representative example of spiral and line drawings from the motor tasks subscales before and after stimulation (clinical scales from patient 14). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, non-significant comparisons are denoted as ns.

76.9 [42.0–122.0]% during active stimulation. Neither differed significantly from baseline (sham: Wilcoxon signed-rank test, $p = 0.36$; active: one-sample t-test, $p = 0.34$), and the comparison between conditions was also non-significant (Wilcoxon, $p = 0.28$). A similar result was found on the least affected side (median values were 93.7 [66.1–110.8]% in sham and 71.2 [47.8–98.2]% in active stimulation), with no significant deviations from baseline (sham: t-test, $p = 0.70$; active stimulation: Wilcoxon, $p = 0.49$) or differences between conditions (paired t-test, $p = 0.65$).

Reduction of aberrant thalamic oscillations

Intracerebral LFPs were recorded before, during and after short-term therapy in patients 8 and 12. Direct assessment of oscillatory activity through VIM LFPs in these two patients implanted with DBS systems offers an exploratory opportunity to determine whether sensory PES may be associated with measurable changes in a canonical tremor-related relay nucleus. Fig. 4a and 4b depict the reconstruction of VIM and the corresponding DBS

lead placement for patients 8 and 12, respectively. The strongest LFP signals were recorded from left channel 0-3 on patient 8 and left channel 1-3 on patient 12, which were therefore chosen for subsequent analyses and recordings.

In the stimulation condition, patient 8 showed 'true' oscillatory activity in the selected channel across the 7.3–26.9 Hz range, defined as frequency bins exceeding the fitted aperiodic 1/f background by at least 0.5 standard deviations. This activity spanned the theta (4–8 Hz), alpha (8–12 Hz), and beta (12–30 Hz) frequency bands. Mean power decreased from 24.3 μV^2 before stimulation to 23.2 μV^2 after stimulation, corresponding to a 4.3% reduction (Fig. 5a). Clinically, FTM severity decreased by 46.2%, while the FTM specific motor tasks subscale decreased by 22.6%. In the sham condition, patient 8 again demonstrated true oscillatory activity in the selected channel within the 7.3–26.9 Hz range. However, mean power increased from 23.3 μV^2 before sham stimulation to 24.3 μV^2 afterward, representing a 4.2% increase (Fig. 5b). Clinically, both FTM severity and the motor tasks subscale remained unchanged from baseline following sham stimulation.

For patient 12, under the stimulation condition, the selected channel exhibited true oscillatory activity between 16.0 and 34.9 Hz, encompassing the beta (12–30 Hz) and gamma (30–125 Hz) bands. Mean power declined from 18.3 μV^2 prior to stimulation to 14.6 μV^2 afterward, representing a 20.3% reduction (Fig. 5c). From a clinical perspective, FTM severity decreased by 40% and the FTM specific motor tasks subscale decreased by 36.8%. In the sham condition, patient 12 again demonstrated true oscillatory activity in the selected channel within the 17.4–38.1 Hz range, spanning the beta and gamma bands. Mean power rose from 13.9 μV^2 before sham stimulation to 15.2 μV^2 afterward, corresponding to a 9.5% increase (Fig. 5d). Clinically, FTM severity decreased by 20%, and the motor tasks subscale decreased by 27.3%.

Modulation of disynaptic group I inhibition

Disynaptic group I inhibition was evaluated using the FCR H-reflex conditioning test paradigm previously described by us for the forearm [20]. Owing to participants' frailty and advanced age, this protocol was restricted to patients 1–9. Assessments were performed both before and after stimulation or sham intervention. To ensure methodological consistency, the amplitudes of the unconditioned FCR H-reflex and ECR response were matched between pre- and post-stimulation recordings. Neither the stimulation nor the sham condition produced statistically significant changes in the amplitude of the unconditioned FCR H-reflex at the post-intervention assessment (fixed effects: condition, $p = 0.63$; time point, $p = 0.25$; interaction, $p = 0.91$), indicating that the reflex response remained stable across time and experimental conditions. Likewise, the amplitude of the unconditioned FCR M-wave did not change significantly (fixed effects: condition, $p = 0.80$; time point, $p = 0.47$; interaction, $p = 0.57$). However, the stimulation condition produced a significant reduction in disynaptic group I inhibition (see Fig. 5e), with a mean decrease of $26.13 \pm 19.16\%$ (one-sample t-test, $p = 0.006$). By comparison, the sham condition resulted in a small, non-significant reduction of $2.70 \pm 12.41\%$ (one-sample t-test, $p = 0.56$). Accordingly, the change observed following stimulation differed significantly from that observed after sham (paired t-test, $p = 0.01$).

Long-term suppression of tremor

Twelve patients also participated in a separate study investigating the long-term effects of two consecutive weeks of personalized PES therapy, combining longitudinal kinematic and clinical assessments with patient-reported outcomes.

A linear mixed-effects model with a random intercept for patient showed significant effects of both time-point and session on the FTM total score. As shown in Fig. 6a, both PRE and POST scores of FTM total progressively decreased across sessions. PRE scores were significantly higher than POST scores ($p < 0.001$), indicating a short-term reduction in tremor following stimulation. Session number also had a significant effect ($p < 0.001$), reflecting cumulative improvement over the two-week intervention. Although scores increased slightly between sessions 5 and 6 after the weekend break, this effect was not significant ($p = 0.09$). By session 10, mean PRE and POST values decreased to $74.57 \pm 17.17\%$ and $68.56 \pm 15.12\%$, respectively. Five days after therapy ended, scores returned to baseline ($95.25 \pm 19.49\%$). A similar pattern was observed for the severity subscale

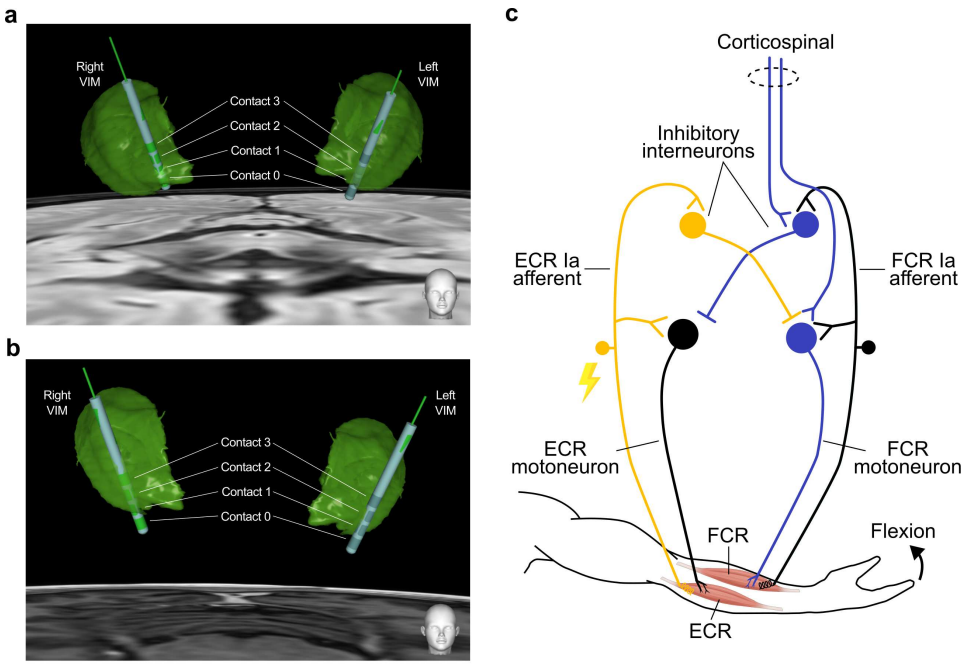


Fig. 4 SureTune reconstruction of bilateral ventral intermediate nuclei (VIM) and corresponding DBS lead locations in patients 8 (**a**) and 12 (**b**), illustrating individualized targeting and final electrode placement within the VIM. **c** Schematic representation of the **hypothetical mechanisms underlying changes in inhibition** following out-of-phase PES. During wrist extension, there is increased inhibition of FCR to facilitate ECR contraction. However, during wrist flexion, this inhibition is reduced to permit effective activation of the FCR. Out-of-phase stimulation (e.g., stimulation of the radial nerve when FCR is contracted) may disrupt this physiological modulation by interfering with the natural firing of Ia afferents, particularly when the muscle is relaxed and lengthening. In this specific case, the interneuron lacks natural excitatory drive from ECR Ia afferents, reducing the effectiveness of the (artificial) afferent input in activating the inhibitory pathway. Naturally active pathways are shown in blue and artificially stimulated pathways in orange.

(Fig. 6b), with higher PRE than POST scores ($p < 0.001$) and significant improvement across sessions ($p < 0.001$). No significant weekend effect was found ($p = 0.12$). By session 10, PRE and POST values had decreased to 77.01 ± 23.51% and 59.49 ± 19.76%, respectively, but returned to baseline five days after therapy cessation (98.89 ± 24.05%). Supplementary videos of patients 2, 3, and 14 performing representative severity subscale items are provided in Supplementary material. For the motor tasks subscale (Fig. 6c), PRE scores were again significantly higher than POST scores ($p < 0.001$), and scores improved across sessions ($p < 0.001$), with no significant weekend effect ($p = 0.18$). At session 10, mean PRE and POST values were 76.42 ± 23.43% and 69.72 ± 18.06%, respectively, returning to baseline after five days (97.31 ± 29.04%). For the functional disability subscale (Fig. 6d), a significant session effect was found ($p < 0.001$), whereas the weekend effect was not significant ($p = 0.98$). By session 10, the mean PRE score had decreased to 73.37 ± 14.85%, but returned to baseline five days later (98.72 ± 16.14%). The percentage reduction in tremor from PRE session 1 to PRE session 10 over the 2-week therapy period, based on the FTM total and its subscales, is presented for each patient in Supp. Fig. 1. CGI-Severity scores also improved significantly after two weeks, with a median reduction of one point ($p = 0.003$). Representative line drawings, spirals, and handwriting samples from participant P14 are shown in Fig. 6e, with additional examples provided in Supp. Fig. 2. Fig. 6f and Fig. 6g further show a shift toward lower tremor severity categories from PRE session 1 (Fig. 6f) to PRE session 10 (Fig. 6g).

Kinematic analyses of the long-term phase showed a trend consistent with the clinical assessments, except for patients 4 and 13. We fitted linear regression models to the RMS of the acceleration modulus obtained from pre-stimulation

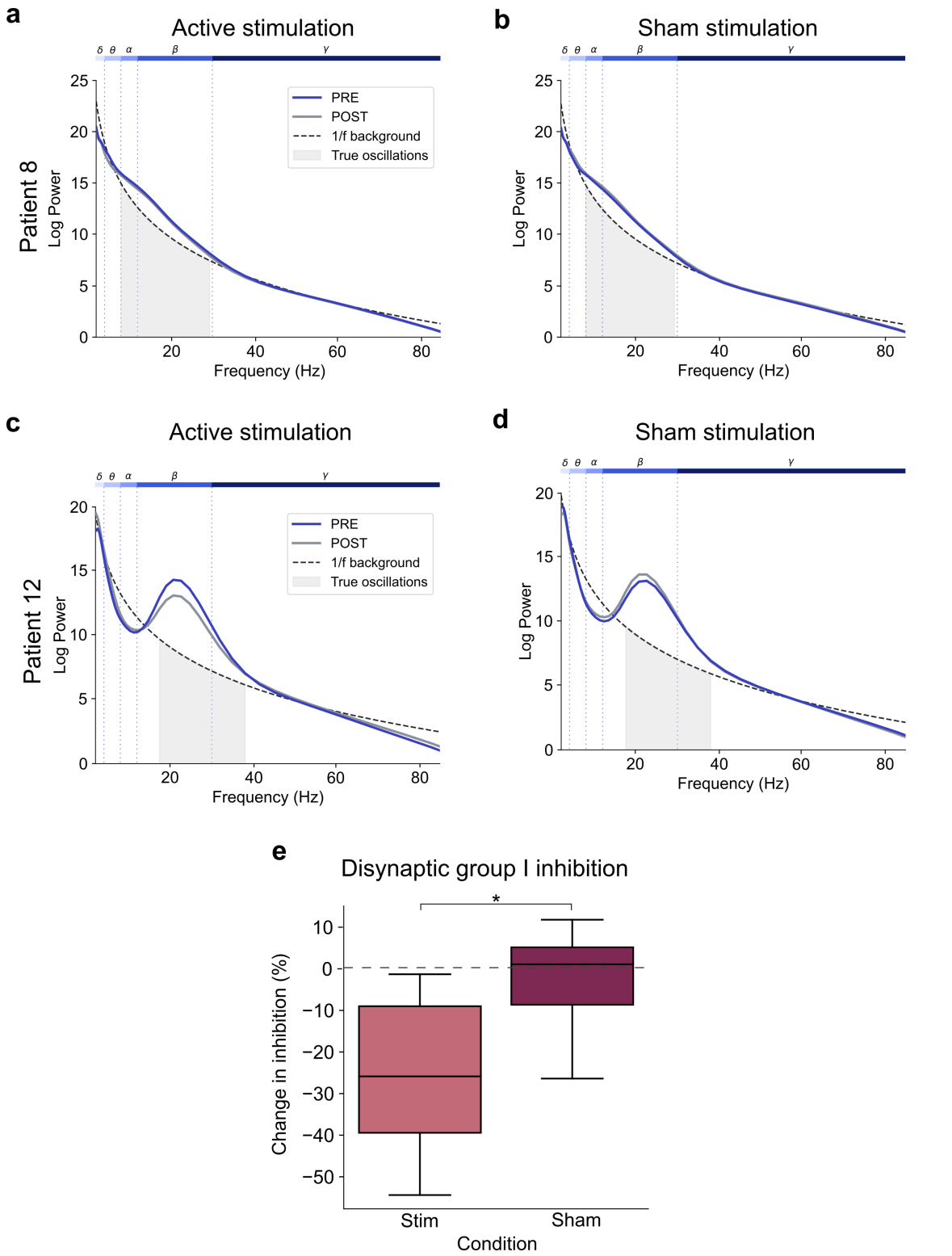


Fig. 5 Neurophysiological assessment results. Power spectra of channel 0–3 left from patient 8 before and after active (**a**) and sham (**b**) stimulation. Power spectra of channel 1–3 left from patient 12 before and after active (**c**) and sham (**d**) stimulation. (**e**) Boxplots representing changes in disynaptic group I inhibition for stimulation and sham conditions (negative values indicate a decrease in inhibition). * $p < 0.05$.

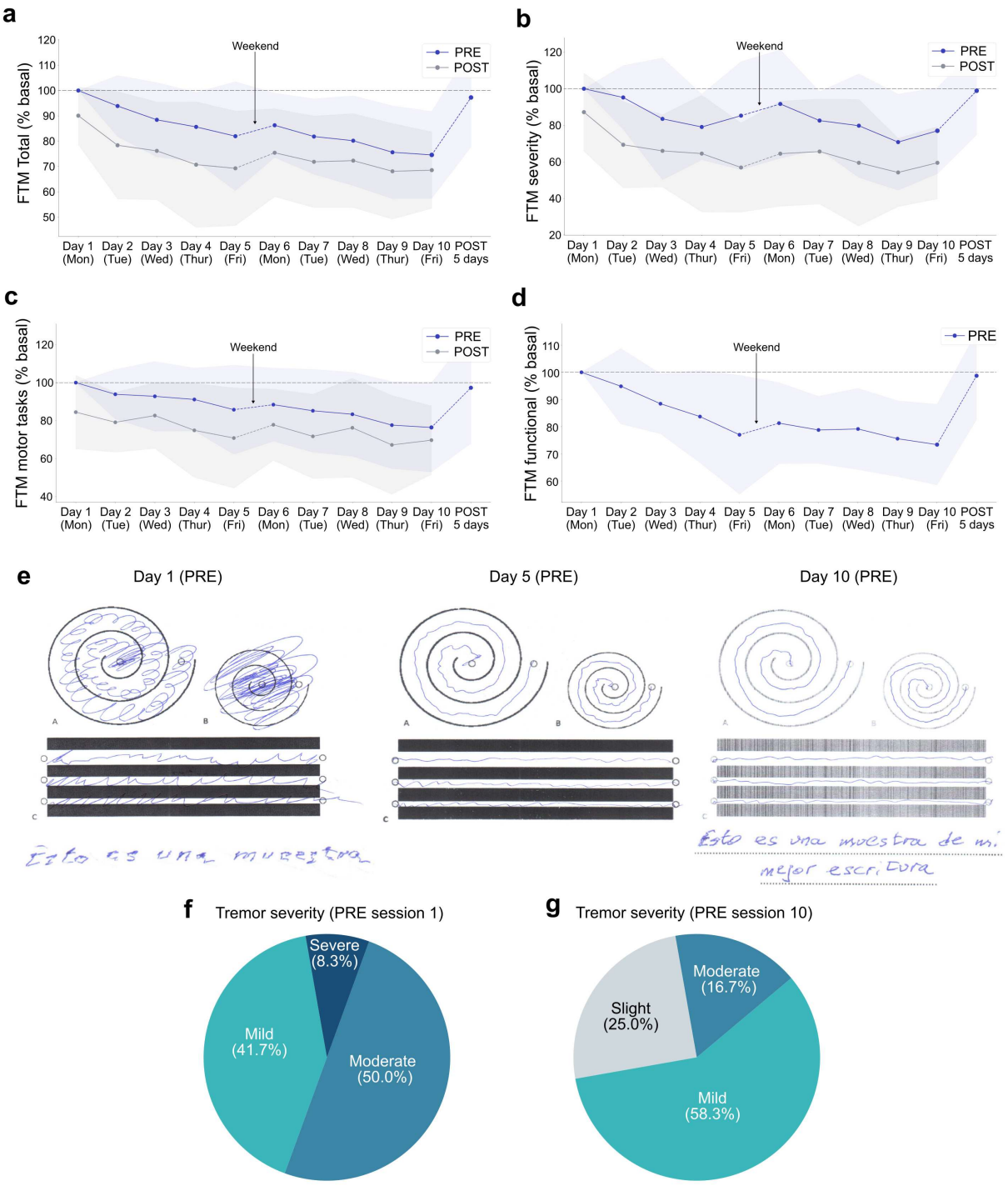


Fig. 6 Results from the long-term clinical assessments. **a** Pre- and post-stimulation evolution of the FTM total score (mean ± standard deviation). **b** Pre- and post-stimulation severity subscale evolution. **c** Pre- and post-stimulation motor tasks subscale evolution. **d** Functional subscale evolution. Note that functional disability subscale from FTM was only assessed before (and not after) stimulation trials. **e** Spiral, line drawings and handwriting example from the motor tasks subscales before stimulation of the first day (PRE session 1), end of first week (PRE session 5), and end of the second week (PRE session 10) (clinical scales from patient 14). **f** Distribution of tremor severity at PRE session 1. **g** Distribution of tremor severity at PRE session 10.

assessments throughout the two-week intervention period, considering both the most- and least-affected sides. Participants were classified as non-responders when all slopes were positive, suggesting a progressive worsening of tremor severity. All other participants were classified as responders. Based on this criterion, patients 4 and 13 were identified as non-responders. Subsequently, statistical analyses were performed using data from the participants classified as responders (Supp. Fig. 3). Based on the hand modulus RMS, there were significant effects of session ($p < 0.001$) and timepoint ($p < 0.001$), with no significant effect of affected side ($p = 0.9533$) or weekend ($p = 0.4219$). By session 10, median PRE and POST values on the most affected side were 54.5 [32.8– 93.5]% and 59.4 [32.5–81.0]%, respectively, while values on the least affected side were 54.1 [42.2–67.9]% and 47.1 [40.1–71.3]%. Supplementary graphs for non-responders are provided in Supp. Fig. 4 and reveal considerable variability in the hand modulus RMS.

Validation and satisfaction with the therapy

Comparison of pre- and post-therapy outcomes on the Bain and Findley activities of daily living (ADLs) scale demonstrated no statistically significant difference following treatment (paired t-test, $p = 0.13$). Mean ADL scores decreased modestly from 36.89 ± 14.11 at baseline to 32.89 ± 18.15 after 2 weeks of therapy. Similarly, no significant change was observed in the Quality of Life in Essential Tremor Questionnaire (QUEST) scores between baseline and post-therapy assessment ($p = 0.09$). The mean QUEST score declined from 30.21 ± 15.11 at baseline to 27.22 ± 16.37 after treatment, representing a mean reduction of 2.99 points, with individual changes ranging from a 14-point decrease to a 7-point increase. Among the 12 participants, four exhibited an improvement exceeding the minimal clinically important difference (MCID) threshold of 4.47 points [21], whereas only one participant demonstrated a worsening greater than the MCID threshold of 4.98 points. Treatment satisfaction, as assessed by the Treatment Satisfaction Questionnaire for Medication (TSQM), was highest in the 'Side Effects' domain (100 ± 0), indicating that no adverse effects were reported during PES therapy. The mean score for 'Global Satisfaction' was 72.2 ± 28.66, suggesting an overall favorable perception of the intervention. The 'Effectiveness' and 'Convenience' domains yielded mean scores of 68.3 ± 23.31 and 66.7 ± 20.29, respectively.

Discussion

Our results showed that sensory PES, synchronized to tremor activity (closed-loop), is an effective, non-invasive method for reducing tremor in patients with ET compared with sham stimulation. Importantly, the clinical benefits were accompanied by measurable neurophysiological changes, including reduced disynaptic group I inhibition after stimulation and decreased oscillatory power within VIM LFPs. Altogether, these observations help connect symptomatic improvement with underlying neural mechanisms of tremor suppression. By demonstrating that PES can modulate both spinal excitability and oscillatory patterns implicated in tremor pathogenesis, these findings provide a basis for the development of more targeted and mechanistically informed stimulation strategies.

A potentially important preliminary observation from two patients is the reduction in thalamic oscillatory power following customized sensory PES, which warrants replication in larger samples. To date, PES-based modulation of thalamic activity has only been examined using intraoperative microelectrode recordings from the VIM during DBS implantation [22]. In that setting, stimulation was associated with increased alpha and beta band oscillatory power, and this increase correlated with tremor reduction. The discrepancy with the present findings likely reflects substantial methodological and physiological differences between studies. First, intraoperative microelectrode recordings and chronic DBS recordings differ in both spatial and temporal characteristics. Microelectrodes capture activity from single neurons or small local populations with high spatial precision, whereas chronic DBS electrodes record LFPs from a broader tissue volume over longer timescales. Consequently, microelectrode recordings may be more sensitive to focal changes in neuronal firing, while LFPs recorded from DBS electrodes more likely reflect large scale network synchronization. Second, the physiological context in which recordings are obtained also differs considerably. Intraoperative recordings are collected during surgery, often under partial sedation or during short periods of wakefulness. Because sedative agents can alter neural activity,

they may change both baseline oscillatory dynamics and responsiveness to stimulation, although their effects may vary across brain regions and remain uncertain in the VIM [23]. In addition, intraoperative findings may be influenced by the microlesion effect, a temporary improvement in symptoms that can occur after electrode insertion. In contrast, the recordings in the present study were obtained in fully awake patients and after any microlesion-related effects had subsided. Furthermore, this study examined changes before and after 20 minutes of stimulation rather than neural responses during stimulation itself. Third, the stimulation protocols were importantly different. In the previous intraoperative study, stimulation was calibrated according to tremor frequency measured before treatment during a postural task and then delivered in an open-loop manner to the median and radial nerves at the wrist. This approach may be less accurate when tremor frequency or phase changes over time, potentially resulting in in-phase (stimulation delivered to the nerve innervating the actively contracting muscle) rather than out-of-phase stimulation. In addition, stimulating both nerves at the same location may increase the overlap in recruited fibers and reduce phase specificity. By contrast, the SATS strategy employed in this study operates as a closed-loop system that continuously adjusts stimulation timing based on ongoing tremor activity detected through EMG feedback. In addition, stimulation is delivered independently to the median and radial nerves. Because open-loop paradigms are more likely to entrain ongoing oscillations, these methodological differences may explain the divergent effects on oscillatory power. Nevertheless, larger studies are needed to confirm the present observations.

Inter-individual variability of VIM-LFPs was also evident. Patient 8 showed little peak oscillatory activity at baseline, which limited the possibility of detecting substantial post-stimulation reductions. In contrast, patient 12 displayed a clearer reduction in true oscillatory activity, particularly within the beta band. These beta band findings are consistent with previous evidence suggesting an important role for beta activity in the VIM [24] [25]. Thalamic beta oscillations are known to decrease during voluntary movement and posture maintenance in ET, and beta suppression has also been observed during passive and active limb movements in the absence of tremor [26]. Such findings suggest that beta activity in the thalamus is state-dependent and decreases during motor engagement. In both PD and ET, beta power in the VIM has been reported to correlate inversely with tremor power, indicating that beta activity decreases as oscillations within the band of tremor frequency (and tremor severity) increase [26]. This suggests a dynamic interaction between beta rhythms and tremor-related activity. Experimental studies support the idea that beta oscillations may play a triggering role in tremor, as beta-frequency stimulation in related subcortical regions has been shown to induce tremor [27]. Within the cerebello-thalamo-cortical network, excessive beta synchrony may therefore facilitate the emergence of pathological tremor, even if beta activity then declines once the tremor becomes established. Consistent with this view, therapeutic interventions such as VIM-DBS have been shown to reduce theta-, alpha-, and beta-band LFP activity in parallel with tremor improvement [25]. In this context, the post-stimulation reduction in beta power observed here may reflect a normalization of abnormal network activity and a lower tendency of the system to enter a tremor state.

At the spinal level, the decrease in disynaptic group I inhibition observed in ET patients following 20 minutes of stimulation is consistent with our previous findings in healthy participants [16]. A similar mechanism may underlie these effects. During wrist extension, inhibition of the FCR is increased to facilitate smooth contraction of the ECR [28] [29], whereas during wrist flexion this inhibition is reduced to permit effective activation of the FCR [30]. Out-of-phase stimulation (e.g., stimulation of the radial nerve when FCR is contracted) may disrupt this physiological modulation by interfering with the natural firing of Ia afferents, particularly when the muscle is relaxed and lengthening (see Fig. 4c). In this case, the interneuron lacks natural excitatory drive from ECR Ia afferents, reducing the effectiveness of the (artificial) afferent input from PES in activating the inhibitory pathway. Collisions between antidromic (stimulation-evoked) and orthodromic (physiological) action potentials may impair normal sensory transmission and, therefore, disrupt natural disynaptic group I inhibition. The absence of comparable changes after sham further supports

the specificity of this effect. Because the spinal cord constitutes the final common pathway through which tremor-related signals reach the muscles, modulation of spinal circuitry could potentially contribute to reduced transmission of pathological oscillations generated upstream, though the precise causal relationship remains to be established. In particular, reciprocal or disynaptic group I inhibitory circuits may serve as a permissive mechanism for tremor expression. High levels of reciprocal inhibition may facilitate tremor by allowing alternating activation of agonist and antagonist muscles, whereas lower inhibition may hinder this rhythmic pattern and dampen oscillatory motor output.

From a clinical perspective, active sensory PES produced significant improvements after a single 20-minute session. Active stimulation reduced tremor by an average of 30% on the FTM rating scale after a single 20-minute PES session, together with a 25.7% improvement in the motor tasks subscale. In comparison, sham stimulation produced only minor changes, likely reflecting placebo effects. These results are particularly relevant, because relatively few studies have evaluated sensory PES using a sham-controlled design, strengthening the methodological quality of the current findings.

Clinical improvements were not fully reflected in short-term kinematic measures, possibly because raw tremor signals showed substantial variability. Unlike bounded clinical scales, kinematic measures have no upper limit and are therefore more sensitive to extreme values and natural fluctuations (see Supp. Fig. 5). Nevertheless, active stimulation showed a trend toward reduced tremor amplitude. Fatigue may also have influenced these recordings. Although EMG median frequency from ECR and FCR did not decrease significantly during the short-term phase (a standard noninvasive biomarker for localized muscle fatigue [31] (see Supp. Fig. 6), the fact that participants repeatedly maintained their arms against gravity throughout the session could have affected tremor independently of the intervention, particularly because kinematic assessments were performed immediately after active or sham stimulation. Furthermore, we cannot exclude fatigue in other, more proximal muscles, which may have contributed to an increase in tremor amplitude.

Our previous study using the SATS strategy in ET reported reductions of 14% with surface stimulation and 64% with intramuscular stimulation [15]. The present study achieved an approximately 30% reduction using surface electrodes, more than doubling the previously reported noninvasive effect. This improvement is likely attributable to the higher stimulation intensities used here (while remaining below MT), which may have enhanced afferent recruitment compared to the prior protocol. Surface stimulation offers important practical advantages, including noninvasiveness, comfort, and ease of application. However, it is less selective than intramuscular stimulation and may recruit deeper neural structures less effectively. Additionally, our previous study examined only unilateral PES, while the current study broadened the scope to include bilateral PES. Importantly, the present study also expanded upon our earlier work by incorporating a sham-control condition and examining potential neurophysiological mechanisms through thalamic recordings and assessments of spinal reflexes.

Significant benefits were also observed after the 2-week treatment. Tremor decreased according to the FTM total score, its subscales, and hand acceleration RMS measurements (in 10 of the 12 identified responders). Hand acceleration was moderately correlated with the FTM severity subscore on the most affected side and highly correlated with the least affected side (see Supp. Fig. 5). The absence of significant short-term kinematic effects may reflect tremor variability or indicate that SATS requires repeated stimulation to consistently reduce movement amplitude. These findings support the possibility that its therapeutic effects accumulate over time.

To our knowledge, this is the first longitudinal study to use sEMG-guided, phase-locked sensory PES to reduce tremor. This strategy represents a closed-loop bidirectional neural interface and reflects the broader transition from fixed stimulation protocols toward adaptive, sensing-based neuromodulation, as showcased recently with adaptive DBS systems [32]. Positive outcomes were observed across clinician-rated scales, kinematic outcomes, patient-reported measures, and treatment satisfaction. The magnitude of benefit was comparable to that typically reported for first-line medications, including propranolol and primidone

[33] [34]. The responder rate was also clinically meaningful, because most participants were refractory to multiple pharmacological treatments. Some non-responders improved during the second week, suggesting that longer treatment periods may be required for certain patients.

Despite these encouraging findings, several limitations should be acknowledged. The sample size was small, especially for the subgroup with VIM-DBS implants (n=2), limiting generalizability and precluding statistical inference for LFPs findings. LFPs recordings were obtained at least two weeks after surgery, but the microlesion effect can persist for three to four weeks in some patients [35], potentially influencing baseline oscillatory activity. Kinematic analyses may have been underpowered to detect short-term effects given the high inter-subject variability. The intervention was also delivered in a hospital setting and over only two weeks, which restricts conclusions regarding long-term efficacy, usability, and adherence in real-world contexts. In this regard, home-based implementations may improve convenience, support longer treatment duration, and allow its use in more ecologically valid settings. Future studies should also address practical challenges, such as how to maintain therapy when tremor becomes too reduced to be reliably detected by sEMG.

In conclusion, sensory PES appears to be a safe, well-tolerated, and effective therapy for ET, likely acting through combined modulation of spinal inhibitory circuits and central thalamic activity. By linking clinical improvements with plausible neurophysiological mechanisms, this study provides a strong foundation for refining stimulation protocols and expanding PES as a treatment option for patients who are refractory to medication, but are reluctant to or are not suitable candidates for invasive procedures.

Methods

Ethics

The study was approved by the Ethics Committees of the Spanish National Research Council (internal codes 225/2023 and 251/2024) and Gregorio Marañón Hospital (records 20/2023 and 18/2024), and was conducted in accordance with the latest revision of the Declaration of Helsinki. All participants enrolled voluntarily, were fully informed about the study procedures and potential adverse effects, and provided written informed consent prior to participation. The primary aim of this study was to evaluate the potential of customized sensory PES to modulate the aberrant neural circuits involved in the generation and propagation of tremor in ET, which arise at the level of the central nervous system. The Spanish Agency of Medicines and Medical Devices did not classify the project as a clinical or interventional trial. Therefore, registration was not required.

Experimental design

The study was structured in two phases to examine both the short-term and long-term effects of PES on tremor. Short-term effects were assessed by comparing the effects of 20 minutes of PES delivered below MT with those of a sham condition. Subsequently, the cumulative long-term effects of PES were evaluated after two weeks of repeated stimulation (see Fig. 1a).

The short-term phase comprised two experimental sessions: one involving active stimulation and the other sham stimulation. The order of the sessions was randomized, and they were separated by at least 48 h to minimize possible carry-over effects. Each session included neurophysiological assessments, consisting of an H-reflex conditioning test paradigm to evaluate disynaptic group I inhibition at the wrist, and LFPs recordings in patients implanted with DBS devices. Kinematic assessments were also performed to quantify tremor using IMUs, along with the administration of clinical rating scales. All assessments were conducted before and after the 20-minute stimulation or sham intervention.

The long-term phase consisted of 10 experimental sessions conducted over two consecutive weeks, from Monday to Friday. In each session, kinematic assessments and clinical scales were administered before and after 20 minutes of stimulation. In addition, participants completed questionnaires assessing quality of life and ADLs at the beginning and end of the two-week intervention. At the end of the study, they also completed a questionnaire evaluating the usability of and satisfaction with the therapy. A follow-up session, consisting on the administration of clinical scales, was conducted five days after the end of the intervention to assess the persistence of treatment effects.

Participants

Fourteen patients with ET were recruited from the Movement Disorders Unit of Gregorio Marañón Hospital (Madrid, Spain) between January 2024 and September 2025. Inclusion criteria were: a clinical diagnosis of ET according to established consensus criteria [1], age between 18 and 80 years, tremor affecting at least one upper limb, and capacity to provide informed consent. Exclusion criteria included the presence of other movement disorders, peripheral nerve injury, pregnancy, anticoagulant treatment, skin lesions that prevented electrode placement, and significant medical comorbidities that could interfere with participation or influence the outcome measures. All participants continued their usual anti-tremor medication throughout the study. Participants were randomly assigned to the different experimental protocols described previously.

For the short-term phase of the study, a sample size calculation was performed assuming a within-subject design in which each participant underwent both stimulation and sham conditions. Based on a clinically meaningful between-condition difference of 30% in tremor reduction, with an assumed standard deviation of 30% for the stimulation condition and 20% for the sham condition, a two-tailed paired t-test with an α level of 0.05 and 80% power indicated that at least nine participants were required. To account for a possible dropout rate of 20%, the recruitment target was increased to 12 participants. Ultimately, 14 participants completed this part of the study (see Supp. Table 1 for demographic details). In addition, short-term changes in reciprocal inhibition were assessed in nine patients (patients 1–9), whereas changes in VIM local field potentials (VIM-LFPs) were evaluated in two patients (patients 8 and 12, see Supp. Table 1).

For the long-term phase of the study, a sample size calculation was conducted using a one-sample design to test whether tremor reduction after two weeks of PES therapy was significantly greater than zero. Assuming a clinically meaningful mean reduction of 40% with a standard deviation of 30%, a two-tailed one-sample t-test with a significance level of 0.05 and 80% power indicated that a minimum of seven participants was necessary. Allowing for a 20% dropout rate, the recruitment target was increased to nine participants. Nevertheless, more patients were successfully recruited, and a total of 12 participants were included in this part of the study (patients 1-5, 7-11, 13-14, see Supp. Table 1).

Neurosurgical procedure and imaging reconstruction

Patients 8 and 12 underwent bilateral VIM DBS for medically refractory ET according to the institutional clinical protocol. Target coordinates were defined relative to the midcommissural point. Bilateral VIM-DBS was performed under local anesthesia using an awake surgical approach. A Leksell stereotactic frame was applied, followed by acquisition of a volumetric stereotactic computerized tomography (CT) scan in the operating room. The CT images were co-registered with preoperative 1.5-T magnetic resonance imaging (MRI) scans, including volumetric post-contrast T1-weighted and T2-weighted sequences, using Brainlab Elements® software. Bilateral trajectories were established using one to three microelectrodes for intraoperative recordings and microstimulation. Permanent bilateral SenSight™ directional DBS leads (Medtronic®) were subsequently implanted. Postoperative CT confirmed accurate lead placement and excluded procedure-related complications. Percept™ PC neurostimulators (Medtronic®, Ireland) were then implanted in the subclavicular region during the same surgical procedure. Preoperative T1- and T2-weighted MRI sequences and postoperative CT images for lead localization were integrated into SureTune™ software (Medtronic®) for anatomical reconstruction. Stimulation and sham sessions were conducted at least two weeks after surgery, once the microlesion effect had subsided and before the initiation of therapeutic DBS programming, thereby avoiding interference with the standard clinical management plan.

Neurophysiological assessments

During the short-term phase, neurophysiological assessments consisting of (1) LFPs recordings in participants implanted with DBS devices, and (2) H-reflex conditioning test paradigm to evaluate disynaptic group I inhibition at the wrist level, were carried out in different subsets of patients, for both experimental sessions.

Local field potentials. LFPs were recorded wirelessly using the BrainSense Survey Indefinite

Streaming mode before and after stimulation or sham. Bilateral VIM-LFPs were recorded in both patients from contact pairs 0–3, 1–3, and 0–2 at a sampling frequency of 250 Hz (see Fig. 1b for a schematic representation, and Fig. 4a and 4b, for reconstruction of the actual DBS lead placement within the VIM for patients 8 and 12, respectively). LFPs data were acquired through the tablet programmer and subsequently transferred to a laboratory computer for offline analysis. JavaScript Object Notation (JSON) files were converted to .mat format using the Percept Toolbox [36] [37]. For spectral analysis, LFPs from each channel were first demeaned and then transformed into the frequency domain using Morlet wavelets. Power spectra were computed across $\log_2$-spaced frequencies ranging from 2 to 128 Hz. For each frequency, a complex Morlet wavelet with four cycles was convolved with the LFP signal. To identify physiologically meaningful oscillatory activity, the Multiple Oscillations Detection Algorithm (MODAL) [38] was used to separate true oscillatory components from the 1/f component associated with background neuronal activity [39]. Power spectra were log-transformed, and the 1/f background was modelled by fitting a linear function in log-log space. Frequency bins with power values at least 0.5 standard deviations above the fitted 1/f background were classified as true oscillations [40]. Adjacent frequency bins exceeding this threshold were grouped into oscillatory bands. Mean power was then calculated for each oscillatory band before and after stimulation (or sham). In addition, these true oscillations were assigned to canonical frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (30–125 Hz) [41].

Disynaptic group I inhibition. Disynaptic group I inhibition was assessed using the flexor carpi radialis (FCR) H-reflex conditioning test paradigm [42] [43] (see Fig. 4c for a schematic of the circuit). Due to age and frailty, this protocol was limited to patients 1-9. During the experiment, participants were seated comfortably in an armchair and instructed to rest the arm most affected by tremor on an armrest, with the shoulder and elbow positioned at approximately 45° and 120° of extension, respectively, and the forearm fully supinated. EMG activity was recorded at 2,048 Hz using a bioelectric amplifier (Quattrocento, OT Bioelettronica, Italy). Bipolar surface electrodes (Ag/AgCl, 2.2 × 2.2 cm; NeuroPlus, Vermed, USA) were placed over the muscle bellies of the FCR and ECR, with an inter-electrode distance of 2 cm, following skin preparation with abrasive paste. A wet wristband served as the reference electrode for all recordings.

Electrical stimuli were delivered through bipolar felt-pad electrodes (7 mm diameter; Digitimer, UK) connected to constant-current stimulators (DS8R and DS7A; Digitimer, UK). The median nerve was stimulated at the cubital fossa and the radial nerve at the spiral groove, with the cathode positioned proximally. Stimuli consisted of 1-ms monophasic square pulses. Unconditioned FCR H-reflexes were elicited by stimulation of the median nerve alone. Stimulus intensity was adjusted to evoke an H-reflex on the ascending limb of the recruitment curve [44], with an amplitude approximately equal to 50% of the maximal H-reflex. Conditioned FCR H-reflexes were obtained by delivering a conditioning stimulus to the radial nerve at an intensity just below MT, at one of three conditioning test intervals: 1 ms before the median nerve stimulus (-1 ms), simultaneously (0 ms), or 1 ms after (+1 ms). Ten repetitions of each condition were delivered in randomized order, with an interstimulus interval of 5 ± 0.2 s to minimize post-activation depression [45].

Throughout the protocol, participants were instructed to perform slight wrist flexion to facilitate the reflex response [46]. The full protocol was repeated both before and after the stimulation (or sham) session. To ensure comparability between pre- and post-intervention recordings, the amplitudes of the FCR H-reflex and ECR response were matched across time points. Raw EMG signals were digitally band-pass filtered using a second-order Butterworth filter (20-500 Hz). Trials were then segmented over a 500-ms window following the median nerve test stimulus. The peak-to-peak amplitude of the FCR H-reflex was measured within the 15-30 ms interval and averaged across the ten repetitions of each condition. Each conditioned H-reflex was expressed as a ratio relative to the corresponding unconditioned H-reflex amplitude. For each participant, the conditioning test interval producing the greatest inhibition at PRE was selected for subsequent analysis. The percentage change from PRE to POST was calculated according to Equation 1:

$$\text{Change } (\%) = \left(1 - \frac{Ratio_{\text{POST}}}{Ratio_{\text{PRE}}}\right) \times 100 \quad (1)$$

where $Ratio_{\text{PRE}}$ and $Ratio_{\text{POST}}$ represent the ratio between the conditioned and unconditioned H-reflex amplitudes before and after the intervention, respectively. Positive values indicate an increase in inhibition, whereas negative values indicate a decrease.

Clinical assessments

At the beginning of every session, in both the short- and long-term phases of the study, each participant was evaluated in their baseline state by a neurologist with expertise in movement disorders. Assessments included the FTM tremor rating scale (covering the severity, motor tasks, and functional disability subscales) and the CGI of severity. At the end of each stimulation or sham session, the FTM severity and motor tasks subscales were re-administered, together with the CGI of change. During the short-term phase, FTM scores were normalized to the pre-intervention value of each session (stimulation or sham) and expressed as a percentage of baseline. In the long-term phase, scores were normalized to the pre-stimulation baseline recorded on the first day of therapy and expressed as a percentage of the initial value. In addition, total FTM scores were classified according to the 0–4 FTM scale into the following categories: 'No tremor' (score = 0), 'Slight' (1–23), 'Mild' (24–46), 'Moderate' (47–69), and 'Severe' (70–92).

Kinematic assessments

Eleven IMUs (Xsens Awinda system, Xsens Technologies BV, Netherlands) were attached to the head, sternum, pelvis, both shoulders, both upper arms, both forearms, and both hands (see Fig. 1b). Data were collected wirelessly at 60 Hz while participants maintained three standardized postures: arms extended forward; shoulders abducted with elbows flexed and hands held at shoulder level; holding two paper cups to the mouth. Each posture was sustained for 40 seconds, and the protocol was performed both before and after stimulation (or sham) sessions (see Fig. 1a). Raw signals were exported using Xsens MVN Analyze Pro 2023.2 to obtain acceleration data. The recordings were manually segmented to retain only the interval during which the participant continuously maintained the target posture, beginning at posture onset and ending immediately before the arms were lowered. Artifacts were detected and removed with a Hampel filter, after which signals were band-pass filtered with a third-order Butterworth filter over the tremor frequency band (3–12 Hz). Subsequent analyses were based on the first 30 seconds of each signal. Trials with fewer than 30 seconds of valid data after artifact removal were excluded. For each trial and side, tremor amplitude was quantified as the root mean square (RMS) of the modulus of the hand acceleration, as it reflects overall hand movement. As the distal segment of the upper limb kinematic chain, the hand is most affected by tremor and represents the primary target for therapeutic intervention. For each participant, the average across the three standard postures was compared before and after stimulation (or sham).

In the short-term phase, tremor metrics were normalized to the pre-intervention value and expressed as a percentage of baseline for both the most and least affected sides. In the long-term phase, tremor metrics were normalized to the pre-stimulation baseline recorded on the first day of therapy and expressed relative to that value. Patients were also classified as responders or non-responders. To determine this, pre-stimulation tremor metrics collected over the two-week intervention period (RMS of the acceleration modulus, for both the most and least affected sides) were fitted with linear regression models, producing two slopes per patient (one for each side). If both slopes were positive, indicating a progressive increase in tremor over time, the patient was classified as a non-responder; otherwise, the patient was considered a responder. A control group of four healthy individuals was used to establish normative values for the RMS of the acceleration modulus. Tremor was considered present when values exceeded three standard deviations above the healthy control mean. Baseline values below this threshold were excluded from further analysis.

Questionnaires to validate and assess the satisfaction with the therapy

To assess the impact of the therapy on ADLs and quality of life, participants completed the Bain

and Findley ADL scale [47] and the QUEST [48] before and after two weeks of treatment. The Bain and Findley ADL scale is a 25-item instrument that evaluates the ease or difficulty with which patients perform a range of daily activities, with particular emphasis on upper limb function. The total score was converted into a percentage, where 0% indicates no disability and higher values reflect increasing impairment. The QUEST is a 30-item instrument specifically designed for individuals with ET. Each item is scored on a five-point scale from 0 to 4, corresponding to how often tremor affects a particular function or gives rise to specific feelings or attitudes, with responses ranging from 'Never' to 'Always'. The questionnaire is divided into five domains: Physical/ADL (9 items), Psychosocial (9 items), Communication (3 items), Hobbies/Leisure (3 items), and Work/-Finances (6 items). Domain scores were expressed as a percentage of the maximum possible score, with higher percentages indicating poorer quality of life in that domain. A total summary score (QUEST summary index) was calculated as the mean of the five domain percentages. To evaluate patient satisfaction with the intervention, the 14-item TSQM [49] was adapted. This version assessed perceived effectiveness, side effects, convenience, and overall satisfaction. Scores were expressed as a percentage of the maximum possible score, with higher percentages indicating greater treatment satisfaction.

Stimulation strategies

Bilateral stimulation was delivered through surface electrodes (diameter: 3.2 cm; ValuTrode Cloth, Axelgaard Manufacturing, Denmark) placed over the cubital fossa and radial groove to stimulate the median and radial nerves, respectively. A common anode (5 x 5 cm; ValuTrode Cloth) was positioned over the olecranon (see Fig. 1b). Stimulation was guided by bipolar sEMG recordings from the FCR and ECR muscles using Ag/AgCl electrodes (2.2 × 2.2 cm, inter-electrode distance 2 cm; Neuro-Plus, Vermed, USA). EMG signals were sampled at 2,000 Hz. Stimulation consisted of biphasic pulses delivered at 100 Hz with a pulse width of 400 μs (see Fig. 1b). Both recording and stimulation were controlled through a custom EMG amplifier integrated with a voltage-controlled stimulator (EAST; OT Bioelettronica, Italy).

At the beginning of each stimulation or sham trial, MTs were determined separately for each muscle and arm. During active stimulation sessions, intensity was set just below the MT. In sham sessions, the intensity was set to zero, although participants were shown blinking blue light associated with active stimulation to preserve blinding. Only active stimulation was applied during the long-term phase; no sham condition was included. Each session comprised 20 trials of 1 minute each, during which participants maintained the postures from the standard kinematic assessment set that elicited the strongest tremor. Participants were allowed to rest as long as needed between trials. In the long-term phase, the severity of tremors diminished in certain participants to the extent that tremors were no longer distinctly observable in standard postures. In these cases, additional weighted postural tasks were introduced to ensure sufficient tremor expression for accurate EMG-based stimulation delivery. These tasks involved holding objects such as crystal glasses or filled water bottles to increase tremor amplitude.

Stimulation followed the SATS strategy (see Fig. 2a) [15]. To minimize contamination of the EMG signals by stimulation artifacts, SATS uses alternating recording and stimulation windows. Each cycle begins with 1 second of EMG recording from the FCR and ECR muscles. The signals are then demodulated (dashed lines in Fig. 2b), and tremor is considered present if the dominant frequency lies within the 3–12 Hz tremor range. If no tremor is detected, a new recording window begins immediately. If tremor is detected, a stimulation window is triggered. During this stimulation window, adaptive thresholds based on the RMS values of FCR and ECR activity from the preceding recording window are compared with a 15-ms RMS measurement. Whenever the activity of either muscle exceeds its corresponding threshold, a stimulation burst is delivered to the nerve innervating the antagonist muscle for 25% of the tremor cycle, as estimated from the previous recording window. This process continues throughout the 4-s stimulation window. At the end of the stimulation window, a new recording period is initiated to reassess tremor and, if necessary, update the adaptive thresholds.

Statistical analysis

Neurophysiological data obtained from LFPs recordings were analyzed descriptively because of the limited sample size (two participants). For disynaptic group I inhibition, changes in inhibition were tested against zero using two-tailed one-sample t-tests, while differences between stimulation and sham conditions were examined using two-tailed paired t-tests. To evaluate the effects of condition and time point on unconditioned M-wave and H-reflex amplitudes, linear mixed-effects models were fitted. Separate models included condition (stimulation vs. sham), time point (PRE vs. POST), and their interaction as fixed effects, with subject entered as a random intercept to account for repeated observations within participants. Normality assumptions were assessed by visual inspection of residual and random-effects Q–Q plots. When significant main effects or interactions were detected, post-hoc pairwise comparisons were performed with Bonferroni correction for multiple testing. To evaluate the effects of condition and time point on the median frequency of the EMG power spectrum, linear mixed-effects models were fitted. Model included condition (stimulation vs. sham), time point (PRE vs. POST), muscle, side and their interaction as fixed effects, with subject entered as a random intercept to account for repeated observations within participants. For the clinical and kinematic outcomes, normalized tremor values were compared with 100% using two-tailed one-sample t-tests, and differences between stimulation and sham were evaluated using two-tailed paired t-tests. The assumption of normality was checked with the Shapiro–Wilk test. When violated, non-parametric alternatives were used.

Longitudinal changes in clinical scales and tremor metrics were analyzed using linear mixed-effects models to account for repeated measures within individuals. Fixed effects included session number, side (most affected vs. least affected), time point (PRE vs. POST stimulation session), and their interactions. A binary variable was also included to account for the weekend break between treatment weeks. Subject was again entered as a random intercept. Model selection was performed by comparing nested models (with and without interaction terms) using likelihood ratio tests. Residuals were visually inspected using Q-Q plots to assess normality. When deviations from normality were observed, a Box-Cox transformation was applied to the dependent variable and the models were refitted. Changes in questionnaire scores and CGI-Severity ratings from PRE to POST the two-week therapy period were analyzed using either a paired t-test or a Wilcoxon signed-rank test, depending on the normality of the data, as assessed by the Shapiro–Wilk test. A Spearman correlation analysis was performed to explore a possible association between the RMS of the hand acceleration modulus and the FTM severity subscores, for the most and the least affected sides independently. A p-value ≤ 0.05 was considered indicative of statistical significance.

Data availability

Part of the recording datasets used in this paper are available in Figshare at https://doi.org/10.6084/m9.figshare.33435955.

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Author contributions. F.O.B. secured funding for the study. F.O.B., C.M.P., J.R.P.S., A.P.V., A.G. and F.G. conceived the study. F.O.B. and F.G. supervised the study. C.M.P., F.O.B. and J.R.P.S. designed the experimental protocol. C.M.P., F.O.B., L.G.G. and C.G.M. carried out PES sessions, and collected neurophysiological and kinematic data. J.R.P.S., E.L.B. and S.S.G. performed clinical assessments and led patient recruitment. C.M.P. performed data and statistical analysis, with input from F.O.B. and A.P.V. C.M.P. and F.O.B. wrote the original draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing interests. F.O.B. and F.G. are named inventors on a USA patent (National Phase in U.S. No. 17/926278, Title "Control method for a neuroprosthetic device for the reduction of pathological tremors") based on International Application PCT/EP2021/063189, which describes a method for controlling a neuroprosthetic device for the treatment of tremor, in particular ET and PD, by intramuscular stimulation of muscle spindles. F.O.B., C.M.P., A.P.V., F.G. and J.R.P.S. are named inventors on a request for grant of a European patent (submission number 300571696, application number EP25382795.0) that describes a system for monitoring and reducing pathological tremor in a user.

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