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Review Article

Non-invasive electrical stimulation of peripheral nerves for the management of tremor

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ABSTRACT

Pathological tremor in patients with essential tremor and Parkinsons disease is typically treated using medication or neurosurgical interventions. There is a widely recognized need for new treatments that avoid the side effects of current medications and do not carry the risks of surgical interventions. Building on decades of research and engineering development, non-invasive electrical stimulation of peripheral nerves has emerged as a safe and effective strategy for reducing pathologic tremor in essential tremor. This review surveys the peripheral electrical stimulation (PES) literature and summarizes effectiveness, safety, clinical translatability, and hypothesized tremor-reduction mechanisms of various PES approaches. The review also proposes guidelines for assessing tremor in the context of evaluating new therapies that combine the strengths of clinician assessments, patient evaluations, and novel motion sensing technology. The review concludes with a summary of future directions for PES, including expanding clinical access for patients with Parkinson's disease and leveraging large, at-home datasets to learn more about tremor physiology and treatment effect that will better characterize the state of tremor management and accelerate discovery of new therapies. Growing evidence suggests that non-invasive electrical stimulation of afferent neural pathways provides a viable new option for management of pathological tremor, with one specific PES therapy cleared for prescription and home use, suggesting that PES be considered along with medication and neurosurgical interventions for treatment of tremor.

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1. Introduction

Essential tremor (ET) and Parkinson's disease (PD) are progressive neurological disorders, which frequently include uncontrollable upper limb tremors [1,2]. For many patients with ET or PD, these tremors limit their ability to perform activities of daily living and diminish their quality of life [3]. Though ET and PD are among the most prevalent movement disorders in adults [4–6] and have increasing incidence due to worldwide aging trends [7,8], there remains a significant gap in available treatments for pathological tremor.

Traditional tremor treatment options, which range from medication to neurosurgical interventions [9,10], are insufficient for many patients. Pharmacotherapy has historically been the first line treatment for both ET and PD, but lack of therapeutic response combined with the complexity of drug-drug interactions and the intolerability of side-effects at the doses needed to control tremor results in many patients discontinuing therapy. ET pharmacotherapy options, which include beta blockers (propranolol), anticonvulsants (primidone, gabapentin, topiramate), and benzodiazepines, are effective for less than 50% of patients with moderate to severe ET [11–13]. Similarly, PD pharmacotherapy, which typically is dopaminergic medication, provides tremor reduction for only 50% of PD patients [14]. Some patients with severe and medically-refractory ET and PD may be eligible for invasive procedures such as deep brain stimulation (DBS) or magnetic resonance guided focused ultrasound (MRgFUS) [15,16]. While these options have greater efficacy, they are costly, carry significant risk, and

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can cause irreversible neurological damage, and as a result have low patient acceptance [17]. There is a need for a safe and reliable first-line therapy option for ET and PD patients that does not incur the side effects of pharmacotherapy or the risks of invasive procedures.

Peripheral electrical stimulation (PES), the application of electrical currents delivered through transcutaneous or percutaneous electrodes to recruit efferent or afferent neural pathways, has been used in research and clinical rehabilitation [18–20]. PES may be able to modulate aberrant neural circuits, such as those observed with pathological tremor, by shifting the neural system's output towards more normal physiological states [21–23]. Recent studies have shown promising evidence about the efficacy of PES for reducing tremor and paved the way for use of PES as a clinical tremor management solution [24].

This article summarizes the results of studies that evaluate non-invasive peripheral electrical stimulation for the reduction of pathological upper limb tremor in ET and PD. While previous reviews have focused on the technical aspects of stimulation [24] and on stimulation in the context of broader wearable technology solutions and robotics [25–28], this review provides a translational perspective and evaluates the clinical readiness for these novel techniques to be deployed into clinical practice. The review first describes the strength of evidence and clinical translatability of state-of-the-art PES systems. The review then provides a summary of the assessment tools used for tremor quantification in PES studies and continues with a compilation of the physiological hypothesis and evidence about the tremor reduction mechanisms. The review concludes with a perspective on the ongoing work needed to advance PES technology into a widely used tremor management solution with high impact in clinical practice. As a first step, it is essential to define the terms used to describe various PES approaches (Table 1; Fig. 1).

2. Landscape of PES solutions for tremor management

Various afferent and efferent PES strategies have been studied for decades and are hypothesized to provide tremor reduction either by disrupting central tremorgenic activity before the pathologic efferent signals reach the muscles or by eliciting muscle activity. Though several of these strategies have been shown to achieve tremor reductions similar to first-line pharmacotherapies, only one is currently available for clinical use. The following section reviews these PES strategies for tremor reduction and describes their clinical availability or suitability for future clinical deployment (Fig. 2).

2.1. Benchtop and in-lab studies of tremor management therapies

Many efferent and afferent PES therapies continue to be researched and require further technological development and more comprehensive larger and longer studies in out-of-clinic environments before they are suitable for clinical translation. Studies of these therapies are discussed below.

Efferent PES, the most common of which is functional electrical stimulation (FES), has been shown to achieve tremor reduction comparable or superior to that of first-line pharmacotherapies, but has technical and safety barriers that limit clinical translation. FES consists of consecutive electrical pulses targeting skeletal muscles to elicit contraction. Prochazka et al. [30,31] first proposed a closed-loop FES system that continuously measured wrist displacement and delivered electrical stimulation to activate a pair of tremorgenic muscles out of phase to the measured tremor. This strategy produced 73% acute tremor reduction. Researchers have since explored other implementations of closed-loop FES, including varying the site of stimulation, exploring alternate feedback signals (e.g., electromyography), and creating new models to drive the stimulation [32–35], and have achieved 67–84% acute tremor reduction. Researchers have also used open-loop FES, wherein antagonist muscles were stimulated simultaneously to produce co-contraction. This strategy increased joint stiffness and thereby reduced tremor acutely at levels near those of closed-loop FES [36,37].

Evidence to date suggests that FES may not be a clinically viable solution for at-home tremor management. FES motor unit recruitment does not follow typical physiological motor unit recruitment order, and continuous application of FES rapidly fatigues the stimulated muscles, may cause discomfort, and hamper the execution of voluntary movements [38,39]. FES studies to date have been small (fewer than 20 patients) single-arm studies, and no studies demonstrating long-term home use of FES have been conducted, possibly due to patient discomfort, fatigue, and technical limitations of translating FES into out-of-clinic settings. Additionally, FES has not been shown to have any lasting tremor reduction, requiring any clinically viable FES tremor treatment to be able to continuously deliver stimulation.

Afferent pathways, which have lower recruitment thresholds than motor axons, can be activated via PES without eliciting a motor response to drive sensory information to the central nervous system and disrupt

Table 1
Definitions of peripheral electrical stimulation approaches.

"Peripheral" versus "Central" electrical stimulation	
Peripheral electrical stimulation (PES)	Electrical stimulation of peripheral nerves to recruit efferent or afferent neural pathways. PES lies in contrast to central nerve stimulation.
Central nerve stimulation	Electrical stimulation of structures of the central nervous system. Methods of central nerve stimulation (e.g., DBS) are out of scope for this review.
"Efferent" versus "Afferent" stimulation	
Efferent stimulation	Electrical stimulation of efferent (i.e., motor) pathways. (Note that in efferent stimulation, the sensory pathways are also stimulated.)
Afferent stimulation	Electrical stimulation of afferent (i.e., sensory) pathways. (Note that afferent stimulation may evoke reflexes that activate or inhibit efferent pathways.)
"Non-invasive" versus "Invasive" stimulation	
Non-invasive stimulation	Electrical stimulation that is delivered transcutaneously.
Invasive stimulation	Electrical stimulation that is delivered using percutaneous or implanted electrodes. Invasive PES methods are out of scope for this review.
"Open-loop" versus "Closed-loop" versus "Calibrated" stimulation	
Open-loop stimulation	Stimulation that is delivered with a predetermined waveform that is independent of any characteristic of the patient's tremor (Fig. 1A).
Closed-loop stimulation	Stimulation whose waveform is adjusted in real-time based on continuous sensing of the patient's tremor (Fig. 1B). Different sensing modalities (e.g., electromyography or inertial measurements units) lead to different control implementations.
Calibrated stimulation	Stimulation with a waveform that is tuned (once, or repeatedly) to match characteristics (e.g., frequency) of the patient's tremor (Fig. 1C).
"Acute" versus "Lasting" effects	
Acute effect	Tremor reduction, measured relative to pre-stimulation levels, that is present while stimulation is applied.
Lasting effect	Tremor reduction, measured relative to pre-stimulation levels, that persists for minutes to hours after the stimulation ends.

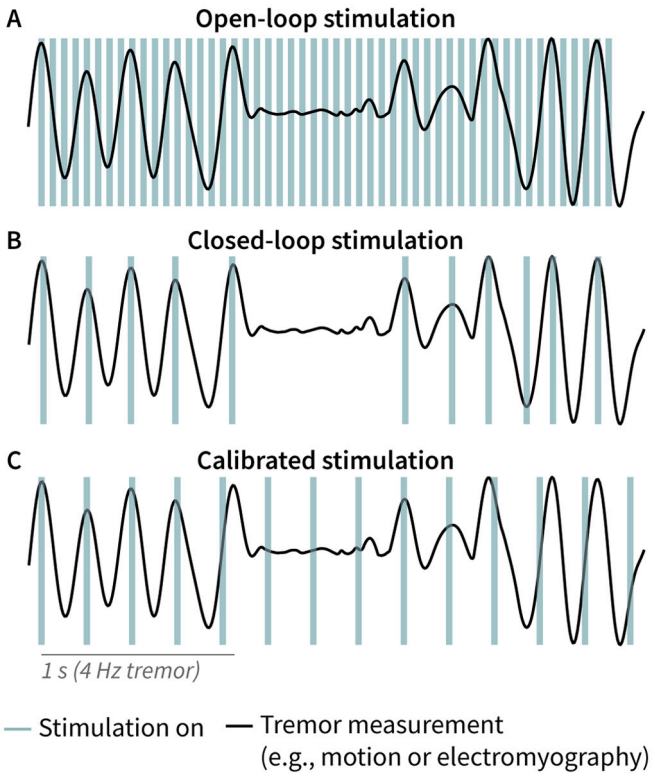

Fig. 1. Stimulation control strategies. Black curves conceptually represent a tremor measurement trace (e.g., wrist displacement or electromyography) and vertical lines represent application of stimulation pulses. (A) Open-loop stimulation is continuously delivered with no relationship to tremor features. (B) Closed-loop stimulation delivers pulses of stimulation that are synchronized with real-time tremor oscillation measurements. If tremor ceases, then stimulation is not applied. (C) Calibrated stimulation is tuned to tremor features, such as tremor frequency, but does not incorporate real-time measures of changing tremor motion. As a result, stimulation may be applied even when tremor ceases.

tremor oscillatory signals before they reach the muscles. Therefore, the application of afferent PES may be able to provide meaningful tremor reduction while overcoming some of the shortcomings of FES [40]. Closed-loop afferent PES strategies typically integrate real-time tremor sensing, e.g., using electromyography or motion measurements, with sensory electrical stimulation (Fig. 1B). Early evidence of the effects of closed-loop afferent PES on tremor reduction were reported by Dosen et al. [34], who synchronized the stimulation to the EMG signals of the antagonist muscle and achieved 42% acute tremor reduction. Other studies have explored closed-loop PES [41–43], with stimulation synchronized to physiological tremor activity and reported 32–54% acute tremor reduction, which lasted for minutes to hours after stimulation was turned off [43,44]. Closed-loop sensory PES approaches have not yet made a clinical impact, as they have only been tested in small (fewer than 15 patients), single-arm, studies and have not yet been studied outside of single-session laboratory environments using benchtop systems to deliver stimulation. Moreover, the amount of tremor reduction with closed-loop PES has varied across studies, presumably because of small sample sizes, the heterogeneity of patients' tremor pathology, and the assortment of stimulation protocols. Closed-loop afferent PES may be clinically viable in the future as a tremor management solution, but increased clinical evidence and development of deployable technologies for accurate and robust real-time tremor sensing and processing are current key barriers limiting out-of-clinic translation.

Open-loop afferent PES (Fig. 1A) overcomes some of the technological barriers of closed-loop afferent PES, since technical implementation is easier, but its effectiveness remains unclear. Studies of open-loop PES of the brachial plexus [45], elbow and wrist flexor and extensor muscles [46–49], and cutaneous afferents at the hand [50–52] have reported anywhere from 0 to 60% acute reduction in tremor in single-session laboratory experiments, most enrolling fewer than 20 patients (largest 34 patients). Thus, it is unclear if open-loop afferent PES will be a viable clinical solution for tremor management.

2.2. *Clinically available tremor management PES therapies*

Transcutaneous afferent patterned stimulation (TAPS) of the median and radial nerves at the wrist [53], a calibrated (Fig. 1C) afferent PES tremor therapy, is the only PES therapy currently approved by the

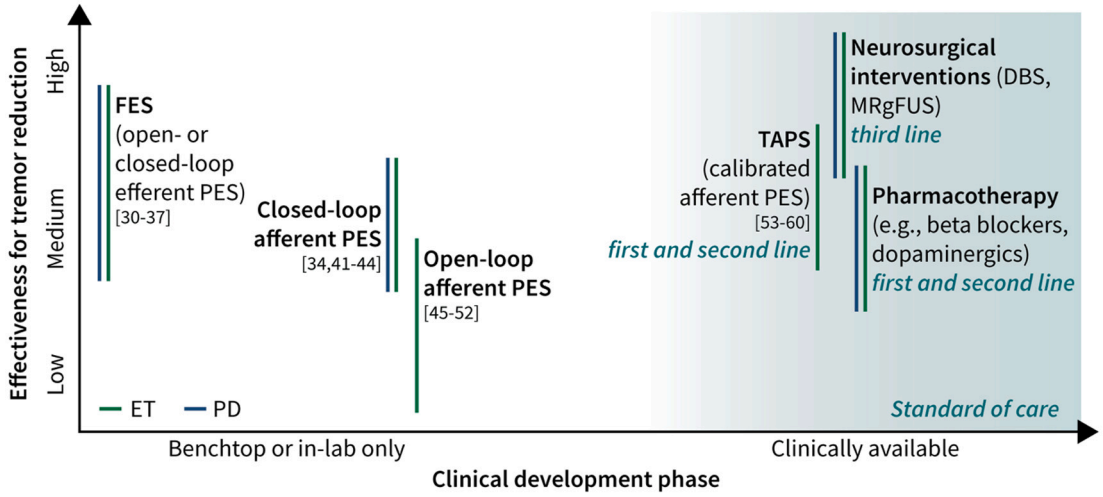

Fig. 2. Landscape of strategies for tremor management. PES strategies were classified by effectiveness and clinical development phase, and the visualized landscape represents a gross placement of these strategies. Effectiveness was estimated as "High", "Medium", or "Low" based on reported tremor reductions, with vertical bar heights loosely representing the range of tremor reductions reported in the listed references. Colour of vertical bars indicate clinical evidence in ET (green) and PD (blue). Clinical development phase was determined based on study designs and regulatory status. Treatment guidelines (e.g., "first line", etc.) for clinically available therapies were determined from International ET Foundation (IETF) guidelines [29]. Abbreviations: PES, peripheral electrical stimulation; FES, functional electrical stimulation; TAPS, transcutaneous afferent patterned stimulation; DBS, deep brain stimulation; MRgFUS, magnetic resonance guided focused ultrasound. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

United States Food and Drug Administration for clinical management of essential tremor (Fig. 2). TAPS doses consist of forty minutes of non-invasive stimulation that alternates between the median and radial nerves at the wrist at a patient's tremor frequency; motion sensors on a wrist-worn TAPS delivery device measure this tremor frequency during an initial calibration [54]. Randomized sham-controlled single-session clinical trials and subsequent longitudinal at-home clinical trials in ET have shown that TAPS therapy provides at least 50% lasting tremor reduction for the majority of patients, with over 90% of patients receiving at least some tremor reduction [53–57]; that tremor reduction with TAPS persists for over an hour after a TAPS dose for many patients [54,56]; and that repeated daily use of TAPS therapy over three months indicated no habituation or dose tolerance-induced loss of tremor reduction [54]. Efficacy of TAPS for tremor reduction was similar between patients on and off tremor medication [54]. The safety profile of TAPS with repeated home use included mild to moderate adverse events such as skin irritation, sores, discomfort, and electrical burns that occurred in 18% of patients in a three-month clinical trial [54]. Efficacy results have been verified with clinician-rated, patient-rated, and objective motion sensor assessments of tremor in over 300 patients, as has safety. Early real world evidence in over 200 ET patients of TAPS for ET confirmed the extensibility of these clinical trial findings into unsupervised, free-living usage environments [58–60].

TAPS is recommended for use in ET as an addition to first-line pharmacotherapies, as an alternative to second-line pharmacotherapies, and before neurosurgical approaches (DBS, MRgFUS) [29]. Patient treatment goals, contraindications, and preference and tolerance for dose-response profiles and treatment side-effects should be considered while formulating a treatment strategy. Future work that expands characterization of TAPS safety and efficacy with repeated home use over longer time periods (i.e., years) would be valuable.

3. Tremor assessment

Tools for assessment of upper limb motor impairment include clinician-rated scales, patient-rated scales, and motion sensor

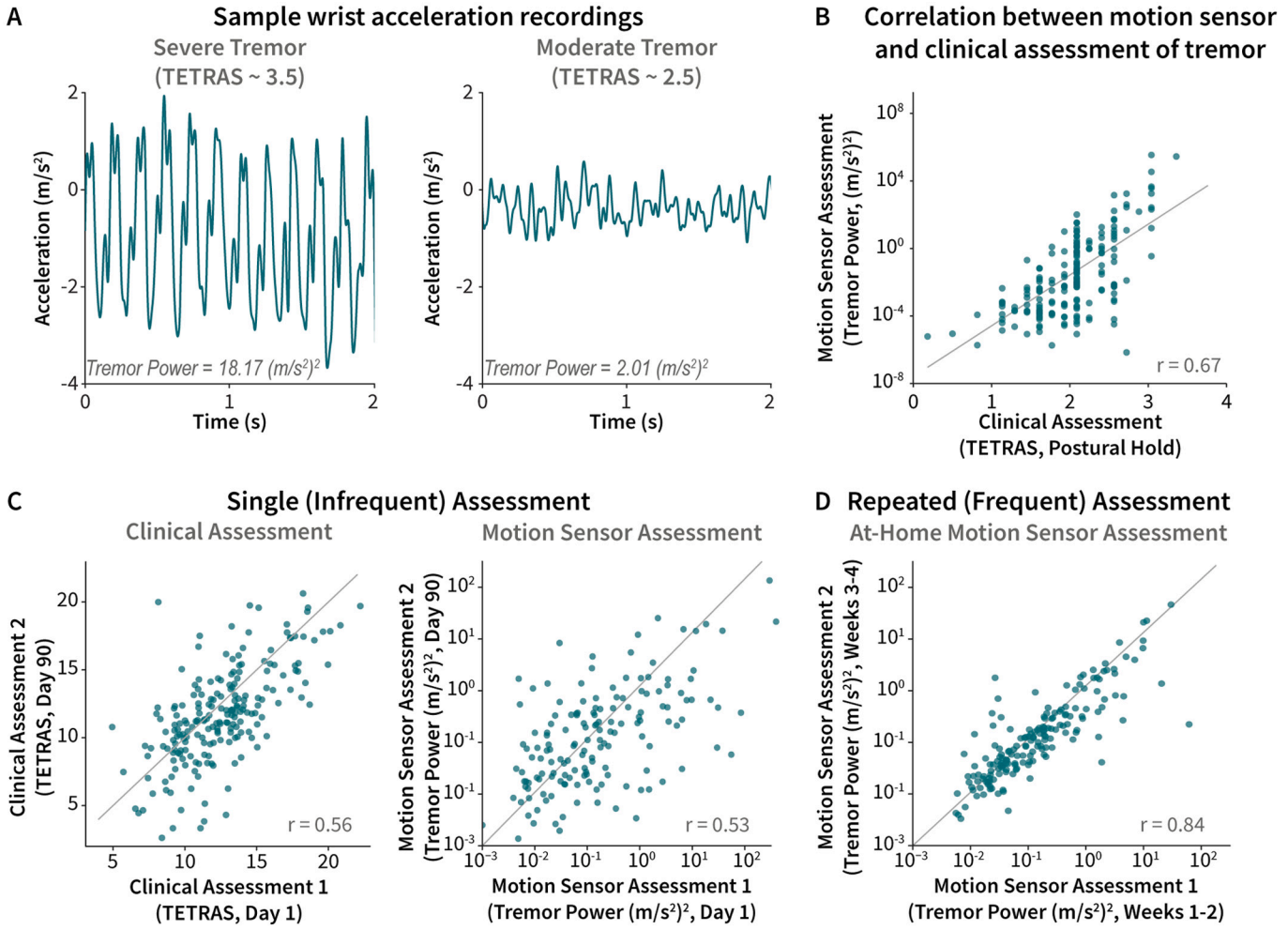

Fig. 3. Motion sensor tremor assessment. (A) Example wrist accelerometry measurements and corresponding tremor power are shown for a patient with severe postural tremor (left) and moderate postural tremor (right). (B) Postural tremor power, computed from accelerometry data, are correlated with simultaneous clinical ratings, suggesting that motion sensors provide a way to remotely monitor tremor severity in free-living settings at many time points. (C) Patients have substantial temporal (within- and across-day) variability in tremor severity. This intra-patient variability limits the ability of a single assessment, whether gold-standard clinical assessment (left) or objective motion sensor assessment (right), to provide a representative quantification of a patient's tremor (across-day correlation coefficients of $r = 0.56$ and $r = 0.53$, respectively). (D) In contrast, repeated daily measurements using motion sensors aggregated over a two-week period at home provide a more robust, quantitative assessment of tremor severity as demonstrated by the higher correlation coefficient ($r = 0.84$). All data are derived from a 3-month clinical study of TAPS [54], which included 263 patients with ET performing a series of three postural holds that were each simultaneously measured by a triaxial accelerometer and rated by clinicians on a 4-point TETRAS scale (A, B), multiple in-person clinical assessments over the 90 days with six assessed TETRAS tasks (for a total clinical assessment score of 0–24), and daily at-home motion sensor measurements (C, D). Panels (A) and (B) adapted from [54]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

measurements. These tools aim to (1) characterize tremor burden, (2) measure the impact of a therapy on the tremor burden, and (3) extract tremor characteristics (e.g., frequency or amplitude) that may be needed to deliver a therapy. This section summarizes tremor assessment tools, outlines strengths and limitations of these tools, and proposes guidelines for using these tools to evaluate therapies.

Scales such as the Tremor Research Group Essential Tremor Rating Assessment Scale (TETRAS) [61], Fahn-Tolosa-Marin Clinical Rating Scale [62], and Movement Disorder Society Unified Parkinson's Disease Rating Scale [63] are among current gold standards for clinical assessment of motor symptoms in ET and PD. These scales assess motor impairment across a variety of motor tasks, typically with clinicians performing a visual assessment to rate each task on a discrete (e.g., 0 to 4-point) scale ranging from "no" to "severe" impairment. While these scales suggest quantitative rating guidelines and have been tested for intra- and interrater reliability within trained raters [64–66], their coarse resolution limits the ability to detect subtle changes in motor symptoms over time or in response to therapy [67]. The need for trained raters to interact with patients limits the number of assessments and does not allow assessments in a free-living setting.

Patient-rated assessment scales, such as the Bain and Findley Activities of Daily Living scale [68], quality of life in essential tremor questionnaire [69], and Parkinson's Disease Questionnaire-39 [70], assess the functional impact of disease symptoms on daily living and quality of life. Patient self-assessments on functional ability and quality of life, arguably, are important outcomes for a therapeutic intervention [71–74] and can be assessed without the involvement of a clinician, which can enable more frequent evaluations. However, similar to clinician-rated scales, these patient-rated scales have limited resolution for detecting subtle and longitudinal changes and have limited reliability.

Motor assessment using inertial measurement units (IMUs) provide an objective means to quantify motor impairment and overcome the subjectivity and reliability limitations associated with clinician-rated and patient-rated scales. IMUs include sensors to track linear motion, rotational motion, and orientation, are readily available in smartphones and smartwatches, and have been integrated into some tremor reduction wearable PES devices [43,54]. Measurements from wrist-worn IMUs (Fig. 3A) have been validated against clinical gold standards (Fig. 3B), and have been used to quantify severity of upper limb motor symptoms in task-based assessments, evaluate efficacy of treatments, and monitor tremor fluctuations longitudinally in free-living environments [54,56,58–60,72,75–83]. The precision and sensitivity of IMU measurements can allow for detection of changes in tremor severity at a finer resolution than clinical scales allow, but can also introduce measurement noise [83]. This measurement noise limits the meaningful resolution of a *single* measurement to be similar to those of clinical rating scales [75,83–86]. More robust tremor assessment can be made by aggregating repeated motion sensor measurements. Other metrics, such as time spent impacted by tremor, have been shown to be related to patient quality of life [87] and can be captured from wearable sensors [78]; these metrics have not typically been used in clinical studies of tremor therapies, but may be valuable to include in future studies.

We suggest two guidelines for tremor assessment in clinical studies and practice. First, characterization of a patient's tremor burden should reflect assessments completed across multiple times and days to mitigate effects of intrapatient variability. A patient's tremor severity can fluctuate considerably within and across days, and can be impacted by stress, caffeine or alcohol consumption, and medication [85,88]. This intrapatient temporal variability limits tremor characterization from a single session regardless of the objectivity of the assessment metric (Fig. 3C). Studies evaluating therapies should aim to include repeated assessments across multiple days to get an accurate assessment of therapeutic effect, including, if possible, frequent repeated wearable-sensor measurements in a home environment (Fig. 3D).

Second, a comprehensive tremor assessment should include clinician, patient, and objective evaluation of tremor. Studies of tremor therapies often use a subset of these assessment tools and have variable reporting methods, which limits comparisons between studies. Moreover, different assessors of tremor severity (e.g., clinicians and patients) do not always track each other well [89]. Future work should continue to develop and validate sensor-derived metrics against clinician-rated and patient-rated to combine the strengths of each (the interpretability and meaningfulness of clinical/patient rating scales, and objectivity and out-of-clinic extensibility of sensor metrics).

4. Neuromodulation mechanisms

Development of PES and other tremor therapies can be accelerated via increased understanding of the pathophysiological mechanisms of tremor generation and reduction. Most first-line pharmacotherapies for tremor, e.g., propranolol (beta blocker for ET) or dopaminergic medication (for PD), are non-specific systemic drugs that have systemic side-effects; though this is not a problem for some patients, these side-effects at the doses needed for therapeutic effect render pharmacotherapy intolerable for many tremor patients. Afferent PES, on the other hand, has potential to specifically disrupt tremorgenic circuits through recruitment of afferent pathways projecting into the tremor oscillatory network. There are two plausible hypotheses of how some afferent PES strategies reduce tremor symptoms. First, afferent fibers activated through PES may reach the tremor sources in the brain and disrupt central tremorgenic activity (Fig. 4, inset A). Second, activated Group Ia and cutaneous afferents (Fig. 4, inset B) could lead to tremor reduction through reciprocal inhibition and disruption of corticomuscular transmission of the tremor drive. We explore each of these below.

4.1. Supraspinal modulation

The contribution of central networks to tremor generation has been established. For instance, it is known that degeneration in the basal ganglia network leads to tremor in PD [90], and that the alteration of the cerebellar circuits is involved in tremor generation in ET [91]. Cerebello-thalamo-cortical circuits appear to be involved in tremor generation for both ET and PD [92]. Lesions or electrical stimulation of nuclei in this cerebello-thalamo-cortical network lead to tremor reduction, suggesting the presence of a complex oscillating network in which afferent inputs play a fundamental role [93,94].

Several studies suggest that tremor reduction with afferent PES is caused by modulation of supraspinal centers in the tremor oscillatory network. Studies of somatosensory evoked potentials [95,96] and neuromodulation techniques [97,98] suggest that afferent PES reaches different brain structures. While median nerve stimulation alters firing patterns in the thalamus and subthalamic nucleus [99–101] and DBS of the ventral intermediate nucleus (VIM) of the thalamus reduces tremor, presumably by selectively inhibiting neurons in the VIM to disrupt cerebello-thalamo-cortical oscillations responsible for tremor [102,103], these studies do not explain why afferent PES has lasting tremor reduction effects [43,44,54,56]. One hypothesis for this lasting effect is that calibrated afferent PES (TAPS) produces a dephasing effect in the thalamus similar to the coordinated reset by DBS [104,105]. Another hypothesis is that afferent PES has a lasting effect on cerebellar circuits that project into the thalamo-cortical network, as supported by the metabolic increase in the cerebellar region measured via Single Photon Emission Computed Tomography (SPECT) imaging after three months of TAPS therapy in 5 ET patients [57]. Purkinje cell degeneration at the cerebellum is one of the main hypotheses for the cause of ET [106] and the cerebellum is involved in motor control and learning by integrating projections from the thalamo-cortical circuit and primary afferents to adjust the motor response. Furthermore, cerebellar injury can lead to pathological tremor, for instance in cerebellar ataxias [107,108], and transcutaneous cerebellar electrical stimulation synced with the tremor phase has been shown to reduce tremor in ET patients

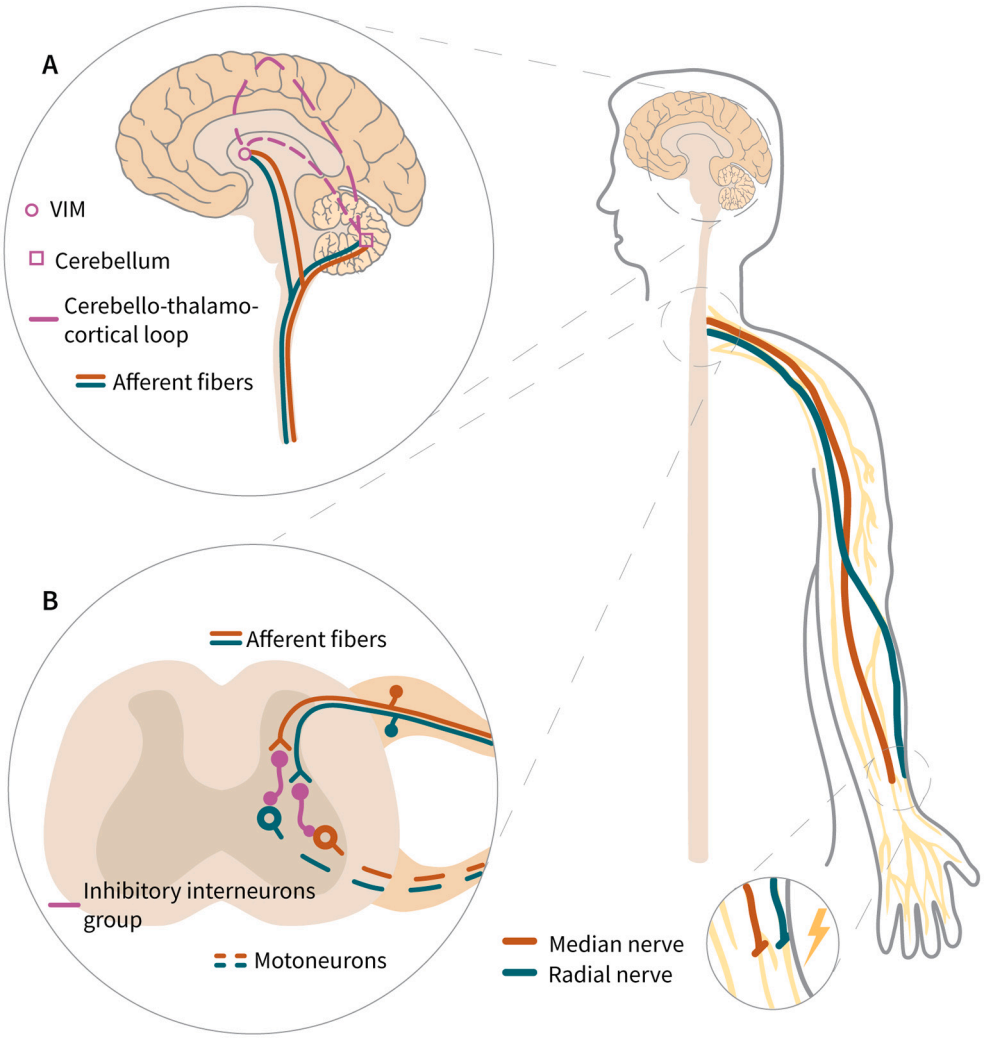

Fig. 4. Schematic of tremor reduction mechanism hypotheses after afferent PES. (A) The afferent fibers activated through PES reach the tremor sources located at the brain, primarily the cerebellum and the ventral intermediate nucleus (VIM), and disrupt tremorgenic activity. (B) The recruited afferent fibers make connections with inhibitory interneurons at the spinal cord, mainly involved in spinal reflexes circuits and/or the propriospinal system, which modulates the supraspinal tremorgenic input and prevents it from reaching the muscles.

[109]. Supraspinal modulation hypotheses are compatible with the use of calibrated open-loop stimulation strategies since accurate timing of the stimulation pulses might not be crucial to reduce tremor.

4.2. Modulation at the spinal cord

Contributions of spinal mechanisms to tremor generation have also been described. For instance, abnormal spinal reflexes have been reported in ET and PD patients, indicating aberrant behavior at the spinal cord [110,111], and the propriospinal system is altered in PD patients [112], potentially contributing to the tremor oscillatory network. Researchers have suggested that central tremorgenic neural activity alone would not explain the observed tremor motion, suggesting that spinal afferents or secondary supraspinal pathways may also input tremor frequency-specific signals to the muscles [113,114]. Group Ia afferents have been proposed to contribute to tremor amplification in a pair of antagonist muscles through monosynaptic reciprocal inhibition [115], a mechanism that afferent PES may use to modulate spinal cord level tremor oscillations. Furthermore, studies using afferent closed-loop PES synchronized to EMG suggest that acute tremor reduction is due to recruitment of these reciprocal inhibition loops, selectively activated with intramuscular electrodes [34,41,42,44,116].

Stimulation of cutaneous afferents have been proposed to modulate the response of propriospinal interneurons [117], which are involved in the corticospinal transmission of voluntary commands [118,119]. Studies have proposed a model of corticomuscular transmission of tremor signals through propriospinal neurons in PD [120]. This model has supported the hypothesis of tremor reduction via stimulation of cutaneous afferents at the hand [50]. Although the hypotheses of spinal modulation through Group Ia and cutaneous afferents might partially explain the acute effects of sensory PES, no evidence has been gathered to explain the relative strength of their neuromodulatory effects and their role in lasting tremor reduction observed in some patients. If tremor reduction is achieved via modulation of spinal reflexes, the use of closed-loop stimulation strategies might be effective due to the recruitment of the afferent fibers that is precisely timed with tremor activity.

5. The future of peripheral electrical stimulation for tremor reduction

A growing body of evidence suggests that afferent PES is a promising new tremor management option for many patients with essential tremor. Some afferent PES therapies have generally positive safety profiles, may directly target the central source of tremor, and have comparable efficacy for reducing tremor to existing standard of care first-line pharmacotherapies (Fig. 2). A calibrated afferent PES (TAPS) is currently available for management of ET tremor, and future work that expands clinical evidence and access for treating tremor associated with PD would be valuable. Closed-loop afferent PES offers promise to become an effective tremor management therapy in the future and would be a good target for expanded clinical research and technological

innovation to support patient-friendly at-home therapy delivery. These advances would enable broader translation of PES into clinical practice and improve care for patients with tremor. Preliminary data from patients using calibrated afferent PES (TAPS) at home suggest that many patients may prefer PES therapy to pharmacological and surgical treatment options [58,59].

A key challenge for management of tremor is navigating the heterogeneous treatment response to both traditional pharmacotherapies and novel PES therapies. Current standard of care typically includes physicians guiding patients through many months of medication trials and dose adjustments before identifying a treatment and dose for sufficient tremor control without intolerable side effects; this process can be very difficult for patients. PES therapies, similarly, have heterogeneous response across patients, and it is likely that patient-specific stimulation waveform and dose (e.g., duration and frequency of stimulation) adjustments can improve per-patient response. Future work to more deeply understand patient subtypes arising from varying tremorgenic pathways, the tremor reduction mechanisms of pharmacotherapy and PES, and relationship between the two [121–123] would be a breakthrough for new treatment discovery and ultimately a better patient experience.

Wearable technologies provide an exciting opportunity to unobtrusively deliver non-invasive PES-based therapy and monitor tremor [25] in a home environment. Non-invasive afferent PES is well-suited for at-home delivery, as peripheral nerve targets are accessible by wrist-worn devices. A calibrated afferent PES (TAPS) wearable device has already been shown in a longitudinal at-home clinical study to be easy to use by patients [54], and wearable technologies likewise could facilitate out-of-clinic translation of closed-loop PES therapies that have currently only been tested in a laboratory setting. Motion sensors, which have been integrated into wearable technologies, enable clinicians to track therapeutic response over months of use, provide a means to overcome the limitations of single-session tremor assessments common to nearly all studies of tremor, and have already generated tens of thousands of tremor assessments in home environments [54,58–60]. These measurements may support discovery of sensor-derived digital biomarkers of tremor subtypes and subsequent research for efficient PES dose, waveform, and delivery refinement to optimize outcome. A wearable technology can then monitor and deliver a personalized therapy, providing a valuable new treatment paradigm.

Finally, this review focused on PES of nerves near the wrist for management of upper limb tremor. The suitability of PES delivered to other anatomical locations for management of other symptoms, including head, voice, and leg tremor in ET and rest tremor, bradykinesia, or freezing of gait in PD, are valuable opportunities to explore further.

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Declaration of Competing Interest

APV has no conflicts of interest to disclose. AR is an employee of Cala Health. SD is a scientific advisor of Cala Health. JP has no conflicts of interest to disclose.

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