

Review

Biomechanical Loading as an Alternative Treatment for Tremor: A Review of Two Approaches

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Abstract

Background: Tremor is the most common movement disorder and strongly increases in incidence and prevalence with aging. Although not life threatening, upper-limb tremors hamper the independence of 65% of people suffering from them affected persons, greatly impacting their quality of life. Current treatments include pharmacotherapy and surgery (thalamotomy and deep brain stimulation). However, these options are not sufficient for approximately 25% of patients. Therefore, further research and new therapeutic options are required to effectively manage pathological tremor.

Methods: This paper presents findings of two research projects in which two different wearable robots for tremor management were developed based on force loading and validated. The first consisted of a robotic exoskeleton that applied forces to tremulous limbs and consistently attenuated mild and severe tremors. The second was a neuroprosthesis based on transcutaneous neurostimulation. A total of 22 patients suffering from parkinsonian or essential tremor (ET) of different severities were recruited for experimental validation, and both systems were evaluated using standard tasks employed for neurological examination. The inclusion criterion was a postural and/or kinetic pathological upper-limb tremor resistant to medication.

Results: The results demonstrate that both approaches effectively suppressed tremor in most patients, although further research is required. The work presented here is based on clinical evidence from a small number of patients (n=10 for robotic exoskeleton and n=12 for the neuroprosthesis), but most had a positive response to the approaches. In summary, biomechanical loading is non-invasive and painless. It may be effective in patients who are insufficiently responsive (or have adverse reactions) to drugs or in whom surgery is contraindicated.

Discussion: This paper identifies and evaluates biomechanical loading approaches to tremor management and discusses their potential.

Keywords: Tremor, biomechanical loading, treatment

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Introduction

Tremor is defined as the rhythmic, involuntary oscillatory movement of a body part.¹ Although everyone exhibits a certain degree of tremor—the so-called physiological tremor—there are a number of pathologies that lead to very disabling tremors. These pathological tremors are the most common movement disorders; their incidence increases with age, and up to 15% of individuals

between 50 and 89 years old are affected.² Moreover, more than 65% of people suffering from upper-limb tremor report serious difficulties in performing their activities of daily living (ADL), thereby greatly decreasing their independence and quality of life.³

Significant effort has been put into developing and improving treatments for tremor. They are currently managed through pharmacotherapy or surgery, consisting either of stereotactic thalamotomy

or, more commonly, deep brain stimulation (DBS). Unfortunately, both alternatives have significant drawbacks: drugs often induce side effects and become less effective over time,⁴ while DBS has the risk of intracranial hemorrhage (~4% of patients) and psychiatric manifestations.^{5,6} Moreover, the percentage of DBS-eligible patients is extremely low;⁷ for instance, only 1.6–4.5% of Parkinson's disease (PD) patients can receive this treatment.⁸ There are currently no effective treatments for the tremors themselves.⁹ Consequently, tremor is not effectively managed in 25% of patients.³⁸ The implications for quality of life and dependency are enormous, and further research and new therapeutic options are needed to manage tremor more effectively.

The effect of mechanical loads on various types of tremor has been described in a large number of studies in the literature. In 1974, Joyce and Rack¹⁰ thoroughly assessed the results of added force and inertia on physiological tremor. Similarly, evidence was found for altered pathological tremor properties due to both inertial^{19–24} and force loading.^{25–30}

Inertial loads are typically applied by attaching a certain mass to the limb, and have been used, to separate the central and reflex components of essential tremor (ET).^{19,21,25,31} This effect had not been reported for PD until recently,²⁰ which led some in the field to view it as evidence of a lack of contribution of reflexes to parkinsonian tremor.³² Inertial loading is thus regarded as a technique to investigate tremor pathophysiology.^{32,34–36} and has been applied to cerebellar tremor,¹⁵ intention tremor arising from multiple sclerosis,¹⁴ psychogenic tremor,¹³ and tremor of chronic alcoholism,¹² among others.

Studies on biomechanical loading, on the other hand, primarily analyze the effect of external forces^{16,25,27,33} and volitional muscle contraction^{26,28–30,37} on tremor. External forces typically consist of a viscous load applied to the tremulous limb,^{15,33,38,42,43} although other studies have investigated the effects of added stiffness^{16,25} or inertia.⁴⁴ Internal forces, i.e., those that originate from muscle contraction, can be either volitionally^{26,28–30,37} or artificially exerted, e.g., through transcutaneous neurostimulation.^{39–40}

Interestingly, many works demonstrate that effective tremor attenuation is attained by appropriate application of internal^{11,29,20,40,41} or external forces^{12,38,45–47} to the affected limb. Biomechanical loading thus emerges as a potential alternative for tremor management, for example, in patients who are refractory to medication. As a consequence, a number of devices have been developed,^{45–51} and some have even reached the market.¹⁷ These systems can be broadly classified as non-ambulatory,^{17,46,51} wheelchair-mounted,⁴⁸ or ambulatory-oriented^{47,49,50} and typically rely on mechanical actuators^{46,47} or dissipative systems^{17,45,48–51} to alleviate tremor. A specific characteristic of this approach is that it is independent of tremor type etiology because it does not act on tremor origin but on its manifestation, which is the appearance of a rhythmic and involuntary oscillatory movement, by changing the biomechanical characteristics of the affected upper limb joint.³⁸

Here we describe two research projects in which two different wearable robots⁹ based on force loading were developed and validated for tremor management. The first consisted of a robotic

exoskeleton^{38,47} that applied forces to the tremulous limbs and consistently attenuated moderate and severe tremors. Despite the system's effectiveness, patients were reluctant to use such a bulky and unaesthetic device as a robotic exoskeleton during their daily life.⁴⁷ Moreover, mild tremors were not attenuated, which was likely due to the difficulty of transmitting low forces to the skeletal system through soft tissues.^{47,52} In order to circumvent these limitations, we developed a neuroprosthesis based on transcutaneous neurostimulation.⁵³ This system successfully alleviated mild tremors, although to a lesser extent than moderate or severe ones, but it moves toward the implementation of a textile-based device that better fulfills patient expectations.

This paper is organized as follows. The robotic exoskeleton is described in the next section, which is followed by a description of the development and validation of the neuroprosthesis based on the results of the first system. The concepts, implementations, and experimental validations are reviewed for both approaches, and then the major findings are discussed. The paper concludes by outlining current and future research in the field of biomechanical loading.

Wearable orthosis for tremor assessment and suppression

In the framework of the DRIFTS (Dynamically Responsive Intervention for Tremor Suppression) project, the wearable orthosis for tremor assessment and suppression (WOTAS) exoskeleton was designed to meet three main objectives: monitoring, diagnosis, and validation of tremor reduction strategies based on biomechanical loading.⁴⁷ WOTAS is an active orthosis (exoskeleton) that can apply intersegment forces when attached to the patient's upper limb (Figure 1). This active orthosis is designed according to the shape and function of the human upper limb; its segments and joints correspond to those of the human body, and its system is externally coupled to the person. It exhibits three degrees of freedom corresponding to elbow flexion-extension, forearm pronation-supination, and wrist flexion-extension. The exoskeleton is activated by a set of flat rotary DC motors (EC 45 Flat Brushless DC motor, Maxon Inc., Sachseln, Switzerland) and harmonic pancake transmissions.⁵⁴ This solution was selected after comparing the available technology for actuation. It is a compact and light alternative suitable for wearable devices.

The mechanical design of the exoskeleton elbow joint is based on a hinge joint, with the axis of rotation placed in line between the two epicondyles. The actuator solution is attached to the structure with its rotary axis aligned with the elbow joint of the exoskeleton. The wrist joint adopted the same solution, but with the axis of rotation placed in the line between the capitate and lunate bones of the carpus. The solution developed for the control of pronation-supination movement is novel and is based on controlling the rotation of a bar placed parallel to the forearm (see Figure 1). The total weight of the entire system is roughly 850 g.

This active orthosis enables both the monitoring of upper-limb movements and the implementation of tremor suppression strategies. Therefore, it is equipped with kinematic (angular velocity) and kinetic (interaction force between limb and orthosis) sensors. The rate of rotation of each activated joint is detected by the sensor system based on a

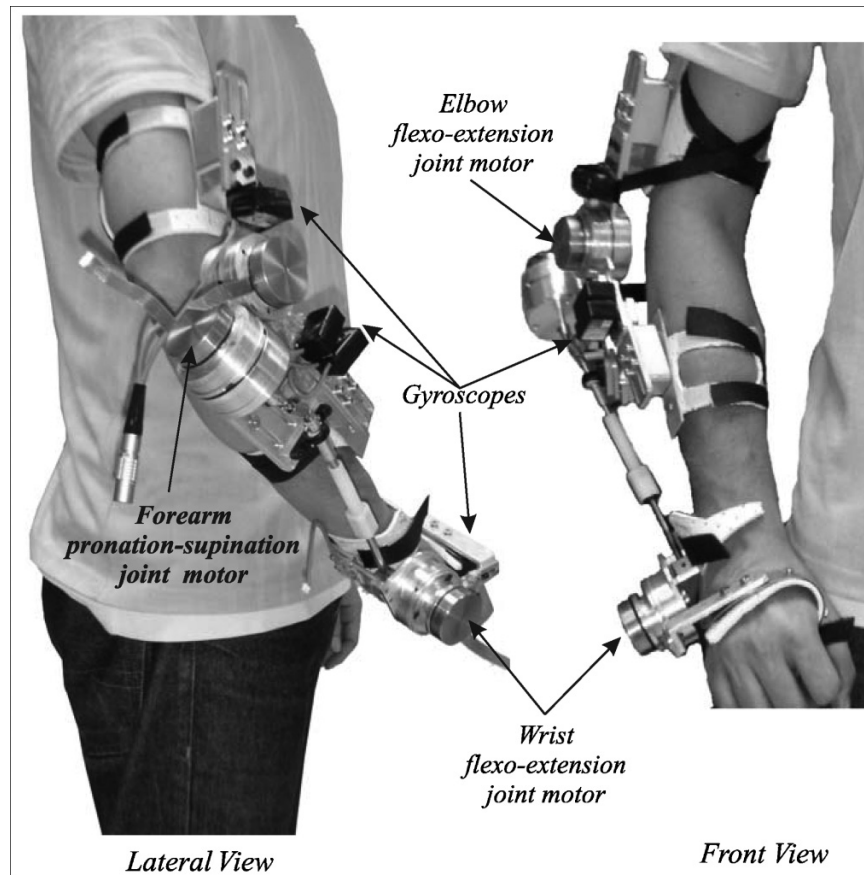


Figure 1. Patient Using the Wearable Orthosis for Tremor Assessment and Suppression Exoskeleton Fixed on the Right Upper Limb. This robotic device spans the elbow and wrist joints. It applies independent tremor suppression strategies to elbow flexo-extension, wrist flexo-extension, and wrist pronation-supination.

combination of two independent chip gyroscopes (ENC-03J manufactured by Murata Inc., Nagaokakyo, Kyoto, Japan) placed distally and proximally to each activated joint. A force sensor based on strain gauges in each joint measures the interaction force between the exoskeleton and the user.⁴⁷ In order to maximize the transmission of forces through upper-limb soft tissues, the orthosis adapts to each patient with low-temperature thermoplastics. In addition, a textile substrate was used to compress the soft tissues and enhance fixation support performance.

Two different control strategies based on biomechanical loading were proposed to suppress tremor:

1) *Tremor reduction through impedance control.* In this approach, the musculoskeletal system (each upper-limb joint contributing to the tremor) is modeled as a second-order biomechanical system exhibiting a low-pass filtering behavior. The cut-off frequency of this second-order system is directly related to the biomechanical parameters of the second-order system, i.e., inertia, damping, and stiffness. Our approach consists of selecting the appropriate modified values of inertia and damping the musculoskeletal system so that the cut-off frequency lies immediately above the maximum frequency of voluntary motion and well below tremor frequency.

2) *Notch filtering at tremor frequency.* In this approach, the exoskeleton actuators generate an equal but opposite motion based on real-time estimation of the tremor component of motion, actively compensating and effectively subtracting the tremor for the overall motion.

Intelligent discrimination between tremor and voluntary motion is a necessary characteristic of any active tremor absorption mechanism. To this end, we proposed a model of tremor motion. The algorithm is based on a two-stage method that estimates voluntary and tremor motion with a small phase lag and was evaluated for 40 subjects with different tremor diseases. The results demonstrated that the algorithm operated correctly and that it is able to estimate the voluntary and tremor components from overall movement with a small phase lag (roughly 1 ms of time delay introduced).⁵⁴

Experimental protocol

The performance of the WOTAS exoskeleton was evaluated in 10 patients with tremor-related diseases. Each patient's pathology was first diagnosed by a neurologist at the hospital; tremor severity was determined using the functional scale proposed by Fahn et al.⁵⁵ Ten users participated in these experiments (three females, mean age

52.3 years). Users presented different pathologies, but the majority were affected by ET, which was moderate in users 1, 3, 4, and 7, and severe in users 2, 5, and 6. User 8 suffered from multiple sclerosis, user 9 from post-traumatic tremor, and user 10 was affected by a cerebellar tremor associated with hereditary ataxia. All subjects provided informed consent. All the experiments were recorded. The users still exhibited tremor despite the regular intake of drugs conventionally administered for tremor. The effects of biomechanical loading were investigated for the upper limb on one side during the execution of different tasks (keeping both arms outstretched, resting the arm on the lap, the finger-to-nose test, and the finger-to-finger test). These tasks have previously been used to characterize tremor movement.⁵⁶

During the experiments, WOTAS operated in three different control modes:

- 1) *Monitoring mode.* WOTAS operates in free mode (no force applied on the upper limb) and monitors subject tremor parameters.
- 2) *Passive intervention.* In this mode, WOTAS can mechanically damp out the tremor movements. This was done by simulating the application of viscosity or inertia to the upper limb to dissipate vibrations caused by the tremor while preserving the user’s voluntary movement.
- 3) *Active intervention.* In this mode, WOTAS is able to apply forces opposed to the tremor movement on the basis of a real-time estimation of the involuntary component of motion. This produces active compensation and effectively suppresses tremor.

The order in which the modes were applied was balanced with Latin squares and the order in which the patients executed the tasks. This approach was adopted in order to avoid interactions and learning effects in the analysis.⁵⁶ Only the operator knew which mode of operation was being applied during the experiments; in other words, the patient, therapist, and doctor did not know whether the orthosis was applying an active or a passive strategy to suppress the tremor or

whether it was working in free or monitoring mode. This approach was adopted to offset the placebo effect.⁵⁶

We analyzed the output voltages from the gyroscopes fitted to the active orthosis (sample frequency 2000 Hz). The figure of merit adopted to quantify the reduction achieved by the exoskeleton is the ratio between tremor power in monitoring mode (P_{mm}) and tremor power in suppression mode (P_{sm}), in either passive or active modes. Thus, tremor reduction was measured under the same user conditions with the orthosis placed on the upper limb. The estimated reduction, then, was the remaining tremor in suppression mode with respect to the tremor in monitoring mode. The parameter selected to compare the tremor level was the power contained in the 2–8 Hz frequency band.⁴⁷

Results

Figure 2 illustrates the effects of WOTAS on tremor movement using both strategies. Figure 2 (left) illustrates the time series corresponding to elbow joint tremor in user 2 while the arm is outstretched. The top part of the figure shows the time signal with WOTAS in monitoring mode. Note that in both passive and active modes, tremor amplitude is clearly lower than in monitoring mode. Figure 2 (right) illustrates the same reduction in the frequency domain. The power spectrum densities (PSD) were obtained from the part of the signal with tremor. The top part of the figure illustrates the PSD of the tremor movement with WOTAS operating in monitoring mode. There is a clear peak of tremor activity near 4 Hz. The middle part shows the PSD while WOTAS was operating in active mode. Note that the energy associated with tremor activity is substantially reduced. In the bottom part of the figure there is also a clear reduction in the energy peak corresponding to tremor activity when WOTAS is in passive mode. These results indicate that WOTAS is able to suppress tremor, and they validate both the active and passive control strategies.

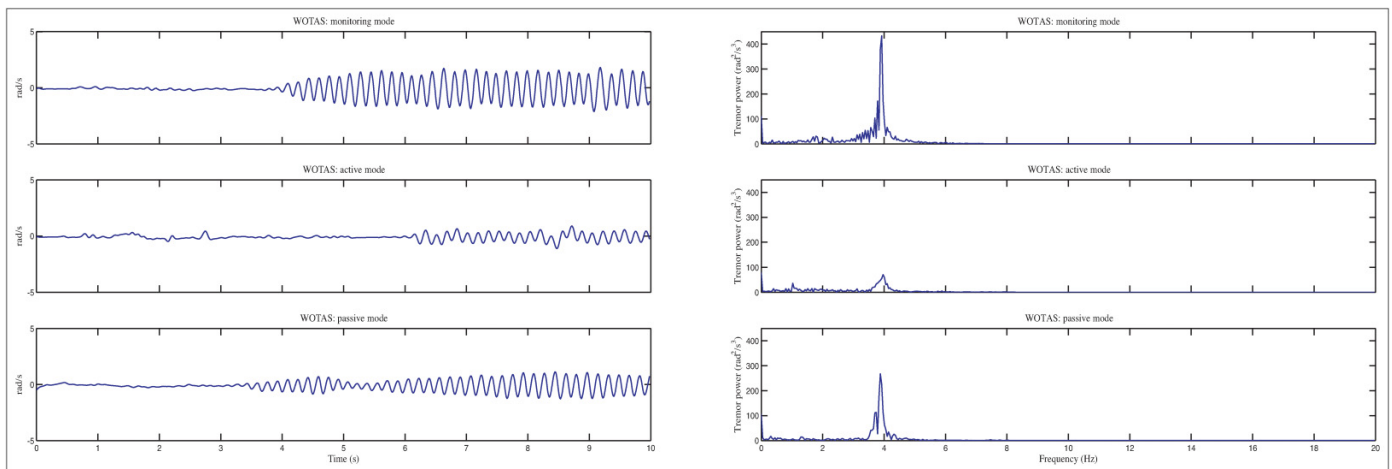


Figure 2. (Left) Oscillations of Elbow Tremor with the Wearable Orthosis for Tremor Assessment and Suppression in Monitoring and Suppression Modes. (Right) Associated Power Spectral Density (PSD) in Monitoring and Suppressing Modes for User 2. Note the sharp reduction in tremor amplitude and power when suppressing actions are applied.

Note that tremor frequency does not change when the exoskeleton is working in suppression modes.

A detailed analysis of the data showed that the active suppression strategy achieved higher levels of tremor suppression (81.2% mean power reduction) than the passive suppression strategy (70% mean power reduction). This suggests that tremor suppression is better in the active mode.

Figure 3 illustrates WOTAS performance for all subjects in suppression mode. Note that exoskeleton efficiency improves with tremor power. A statistical analysis was run to characterize tremor suppression. Thus, it is possible to identify that the robotic exoskeleton has a minimum tremor suppression limit, i.e., if the spectral density of tremor movement is below the lower limit of $0.15 \text{ rad}^2/\text{s}^3$, WOTAS is not effective in suppressing tremor. These lower limits for tremor suppression are mainly related to the interface of the orthosis with the upper limb because stiffness between the orthotic device and the body is a key factor for controlling a dynamic process like a tremor. Therefore, the characteristics of transmission through soft tissues an important role in the efficiency of tremor suppression.

The results also indicated that the range of reduction in tremor energy for signals above this orthosis operational limit is from 3.4% to 95.2% with respect to energy in the monitoring mode. Thus, the device could achieve a consistent tremor power reduction of 40% for all patients and a reduction ratio on the order of 80% of tremor power in specific joints of the patients with the most severe tremors. In one patient, the reduction of tremor in the wrist and elbow was associated with a possible increase in tremor intensity at the shoulder level. However, in the majority of patients there was no visible displacement of tremor movement from the distal to proximal joints (phenomenon distal to proximal tremor shift [DPTS]).

There are hints that mechanical tremor suppression could produce “positive” feedback to ET patients. Patients reported that when they realized that the orthosis was suppressing tremor they *felt more and more confident to accomplish the task*. This was described by patients with severe tremor and requires further research to be confirmed.

Overall, patient tolerance was good. No lesions were observed on the skin, except for a moderate and transient change in skin aspect due to the pressure of the orthosis. Some patients reported slight

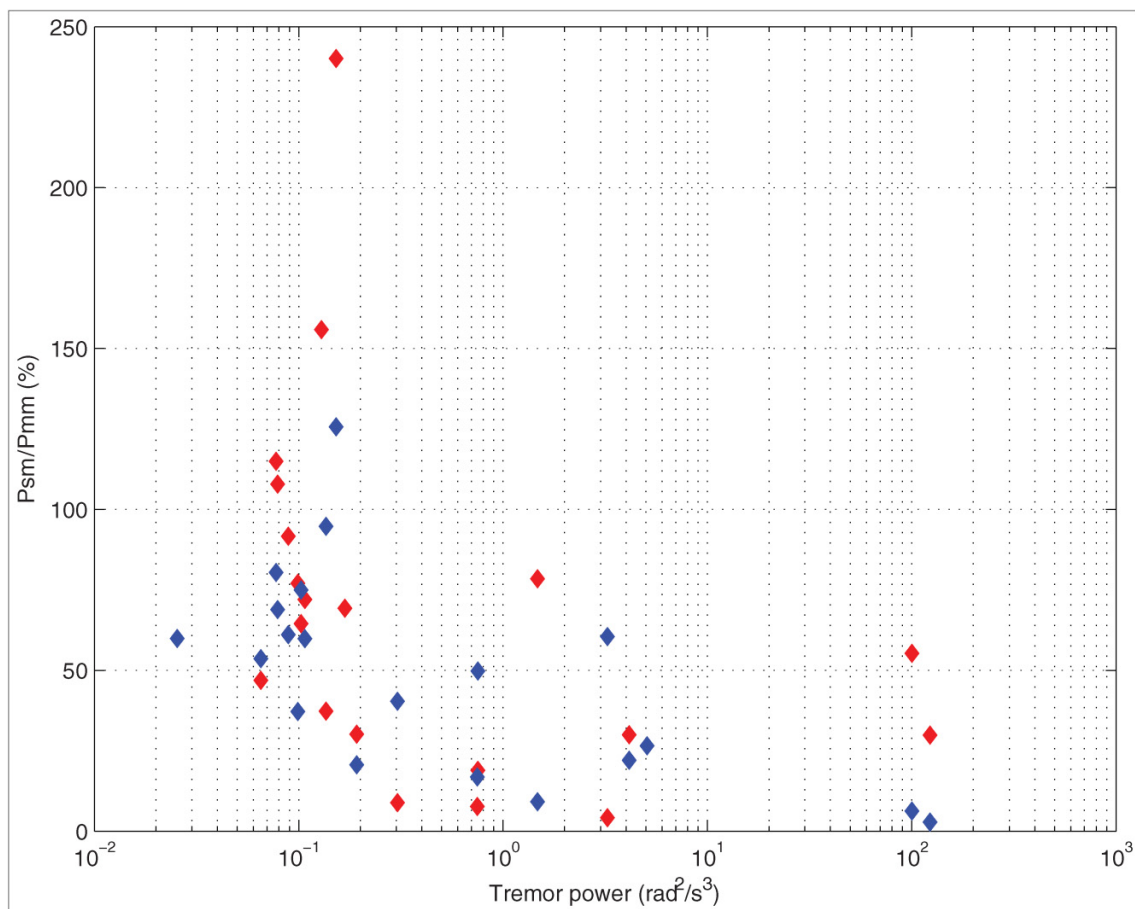


Figure 3. Tremor Reduction (y-axis) Achieved by the Wearable Orthosis for Tremor Assessment and Suppression (WOTAS) Operating in Active (Blue Markers) and Passive (Red Markers) Suppression Modes. The x-axis represents the user’s tremor energy with WOTAS in monitoring mode.

discomfort. These results suggest this new technique as a possible therapy for tremor suppression in human disorders characterized by postural/kinetic upper-limb tremor. It opens up possibilities for disabling forms of tremor, such as that observed in cerebellar and/or brainstem disorders.

Discussion and conclusions

The results of the experiments indicated that the device could achieve a consistent 40% power reduction in tremor for all users and a reduction ratio on the order of 80% in specific joints of users with severe tremor. In addition, users reported that the exoskeleton did not affect their voluntary motion. These results indicate the feasibility of tremor suppression through biomechanical loading. Nevertheless, the approach to mechanical suppression of tremor by means of orthotic devices presents limitations, mainly due to the physical interaction between the exoskeleton and the human limb:

- 1) The transmission of forces through soft tissues plays an important role in tremor suppression efficiency. Wearable devices have a physical limitations for tremor suppression due to force generation (size and power consumption of the actuators) and transmission through soft tissues.
- 2) Emerging actuator technologies, i.e., magnetorheological fluid (MRF) actuators, electroactive polymer (EAP) actuators, and ultrasonic motors, were evaluated for an orthotic implementation. It was concluded that, despite the success of the approach, there is no suitable actuator technology in terms of cosmetic, aesthetic (low weight, compact enough to be worn beneath clothing), and functional (torque, bandwidth)^{18,47} requirements.
- 3) Patients reported that these bulky exoskeletons could not be considered as a solution to their problem because the use of such a device would cause social exclusion.

In summary, robotic-based solutions have clinically validated the biomechanical loading. However, these solutions are bulky and unattractive, and patients are especially reluctant to use them.

Ambulatory tremor suppression system based on functional electrical stimulation

In the framework of the TREMOR project (EU-ICT-2007-224051), a neurorobot was developed to circumvent the major limitations identified in the WOTAS exoskeleton described in the previous section. We elected to use transcutaneous neurostimulation as a means of generating biomechanical loading to the tremulous limb.⁵³ Transcutaneous neurostimulation directly activates the motoneurons (and reflex pathways) of the targeted muscles.⁵⁷ In spite of its inherent limitations in terms of selectivity,⁵⁸ discomfort,⁵⁹ and muscle fatigue,^{60,61} Prochazka and colleagues^{39,40} have already demonstrated that transcutaneous neurostimulation constitutes a feasible approach to tremor attenuation. The TREMOR neuroprosthesis uses transcutaneous neurostimulation as a means of applying internal forces to the tremulous limbs. Moreover, it was possible to replace the rigid mechanical exoskeleton with an active garment that could potentially fulfill users'

expectations and also lead to a future system that could be worn under clothing.⁵³ This immediately overcame the major drawback of WOTAS: its bulkiness.

The TREMOR neurorobot utilizes closed-loop transcutaneous neurostimulation to apply mechanical loads in order to alleviate upper-limb tremor. The neurorobot drives wrist flexion-extension and elbow flexion-extension; pronation-supination is not targeted because of the difficulty of using transcutaneous neurostimulation on muscles that elicit supination due to from the above-mentioned selectivity issues. Therefore, neurostimulation was delivered at the following sites: flexor carpi radialis, extensor carpi ulnaris, biceps brachii and triceps brachii (lateral head). An independent multichannel unipolar neurostimulator (Una Systems, Belgrade, Serbia) controlled each pair of antagonists; common electrodes were placed at the distal third of the forearm and close to the olecranon process. The system is shown in Figure 4.

Neurostimulation was modulated based on instantaneous tremor characteristics, which are estimated from solid-state gyroscopes based on a two-stage algorithm.⁶² Each targeted movement was measured with a pair of gyroscopes using a differential configuration.^{62,63} The two-stage algorithm, built upon that implemented in WOTAS, separates the volitional and tremor components of movement based on their different frequency content, and given that they are additive,^{63,64} it then estimates the instantaneous amplitude and frequency of the tremor with an *ad hoc* Kalman filter⁶² and a weighted frequency Fourier linear combiner.⁶⁴ The algorithm introduces no delay and accurately tracks tremor parameters.⁶² The interaction of the system with the patient is through a multimodal interface that integrated this approach with simultaneous electroencephalography (EEG) and electromyography (EMG) recordings⁶⁶ (Figure 5). In such an approach, EEG is used to determine that the user intends to perform a voluntary movement and to trigger the system. The multichannel surface EMG then detects tremor onset together with its features (at muscle level),^{67,68} and neurostimulation starts. Gyroscope information is used to drive the neurostimulation, given that EMG suffers from electrophysiological artifacts due to the effect of the injected current.⁶⁹

Two control strategies, following the same concept as for WOTAS, were implemented:

- 1) *Tremor reduction through impedance control.* Joint impedance was altered by co-contracting the antagonist muscles through transcutaneous neurostimulation, which affects both viscosity and stiffness because they are monotonic functions of muscle activation.⁷⁸ This attenuated the tremor because the intrinsic cut-off frequency of the muscles (their natural response resembles that of a low-pass filter^{47,70}) was decreased, which filtered the tremor without a great impact on volitional muscle activity. The relationship between the degree of co-contraction and real joint stiffness and damping is not modeled because of the intrinsic complexity of the problem—an adaptive, personalized, and time-varying approach would be needed.⁷¹ This strategy resembled the application of joint viscosity with WOTAS.
- 2) *Notch filtering at tremor frequency.* In this approach, the muscles are driven in such a way that they generate a contraction pattern that

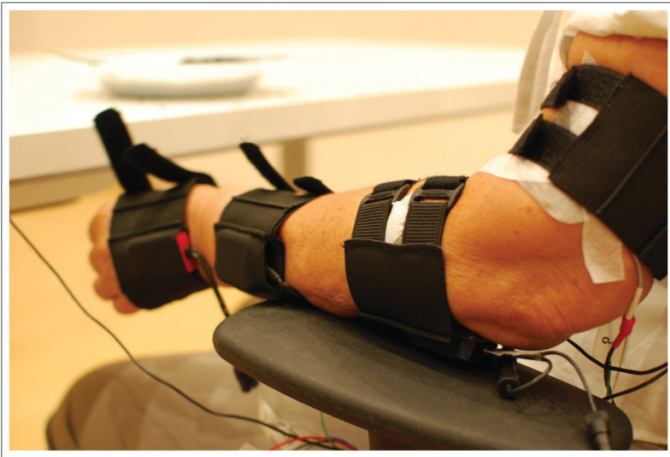


Figure 4. A Patient Wearing the Current Prototype of the TREMOR Neurorobot. The picture shows the four textile substrates containing the inertial sensors and, under them, the neurostimulation electrodes fixed with surgical tape.

opposes the tremulous component of movement. Therefore, the control action resembles a selective filter that only cancels the concomitant tremor.

The current injected in both strategies is modulated based on the tremor parameters in the last period, which provides the controller with a certain predictive nature, thereby minimizing its adaptation to tremor variations. The control algorithm is built upon a rule-based proportional integral law, which partly compensates the non-stationary muscle response to neurostimulation.⁷²

Experimental protocol

We evaluated TREMOR neuroprosthesis performance in 12 patients (10 male, 2 female) exhibiting wrist tremor originating from either PD ($n=3$) or ET ($n=9$). Mean age was 54.1 ± 17.5 years (ranging from 22 to 70). Tremor intensity varied from mild to severe (Fahn–Tolosa⁵⁵ score ranged from 2 to 30). Medication was not interrupted for the recordings. All patients provided informed consent.

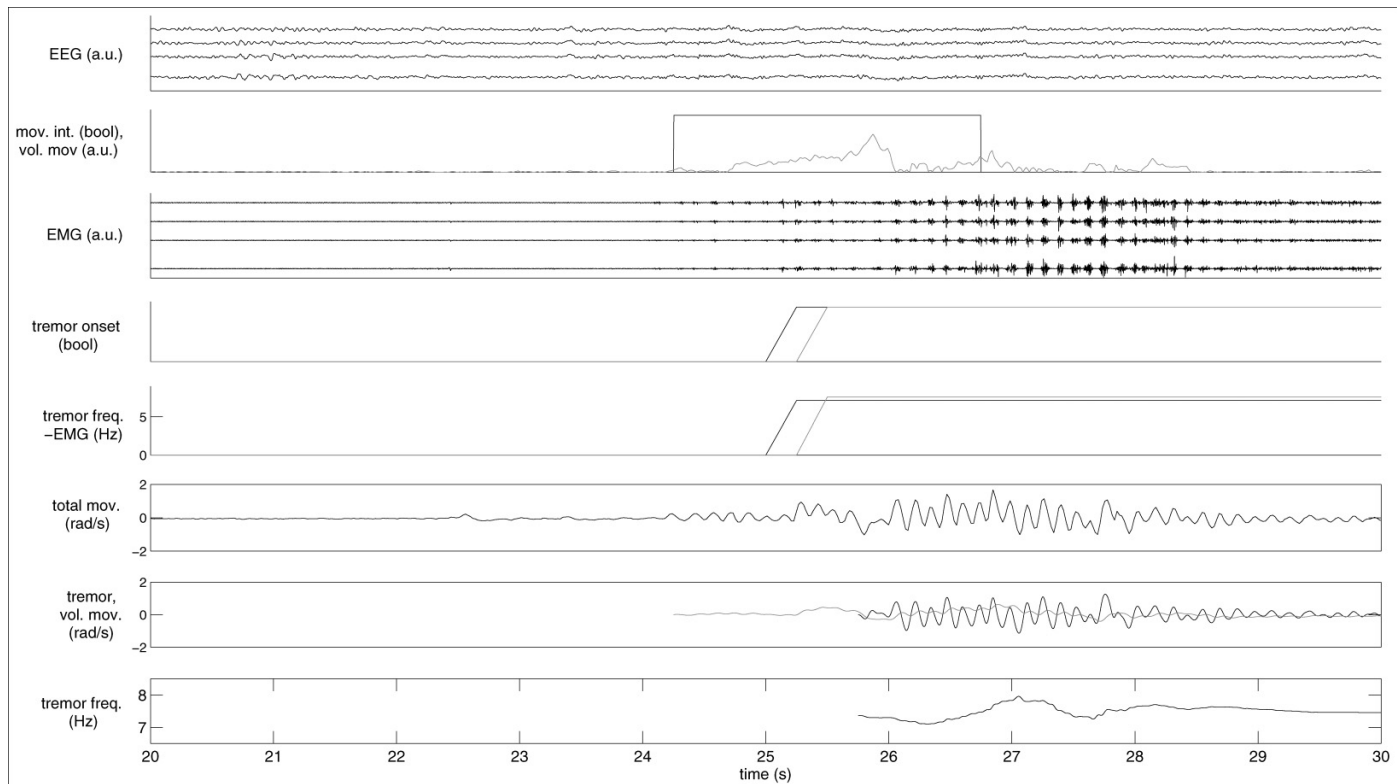


Figure 5. Example of the Multimodal Human–Robot Interface to Characterize Tremor in the Presence of Voluntary Movement in a Tremor Patient. They show, from top to bottom: 1) Four EEG channels, 2) the detection of movement intention from EEG (black) together with the processed voluntary movement (gray), 3) Four surface EMG channels, 4) the detection of tremor onset from surface EMG (wrist extensors and flexors in black and gray, respectively), 5) estimation of tremor frequency from surface EMG (wrist extensors and flexors in black and gray, respectively), 6) wrist flexion-extension measured with a pair of gyroscopes, 7) estimation of voluntary movement (gray) and tremor (black) with the two-stage algorithm, and 8) estimation of tremor frequency with the two-stage algorithm. Reprinted from Ref. 66.

The ethical committee of the Universidad Politécnica de Valencia approved the experimental protocol.

The experimental protocol comprised two major phases: 1) the calibration of stimulation parameters for each user and 2) the tremor suppression experiments. The calibration aimed at tailoring the stimulation levels to the particularities of each user (type of muscle fibers, obesity, definition of motor stimulation threshold, and maximum levels of comfortable stimulation).

The calibration process for the passive strategy was defined as follows: first we looked for the maximum amplitude during independent muscle stimulation and starting from the 75% of these maxima, we looked for the maximum values during co-contraction. This amplitude defined the saturation level in the controller for every muscle, and could be done easily and quickly.

The calibration of the active strategy involved determining controller saturation. We proceeded as follows: we looked for the maximum amplitude during independent muscle activation and starting from this value, we increased the stimulation amplitude in order to generate an oscillation with an amplitude considered by the experimenter to be maximal, typically over that of the tremor. We chose conditions (e.g., limb pose, postural, or rest conditions) that minimized the tremor.

The effects of both control suppression strategies were assessed under the condition(s) where the tremor was most evident (e.g., keeping both arms outstretched, resting the arm on the lap, the finger-to-nose test, and the finger-to-finger test). The subjects sat comfortably in an armchair during the entire recording session. Tremor was assessed in the most affected limb. All trials (the three modes described next) were split into two periods for post hoc analysis: the first one was always without neurostimulation, and neurostimulation was delivered (following one of the two approaches) or not during the second one depending on the type of trial.

The system was operated, as for WOTAS, in three different control modes (types of trials):

- 1) *Monitoring mode.* No neurostimulation was delivered to the muscles.
- 2) *Passive (semi-active) intervention.* The TREMOR neuroprosthesis applied the strategy to attenuate tremor through impedance control.
- 3) *Active intervention.* The TREMOR neurorobot applied the strategy to stimulate the muscles in counter-phase to the tremor.

The order of the trials was alternated in a balanced way to avoid a possible placebo effect;⁵⁶ the experimental design was based on Latin squares. In total, each patient performed between 12 and 30 repetitions in different experimental sessions. Some patients were asked to count back mentally during the tests to exacerbate their symptoms,⁷³ and PD patients were asked to count out loud backwards at the beginning of the session.⁷⁴

Neurostimulation was delivered by unipolar, charge-compensated, pulses. The following parameters were employed: $f=30$ pps, $T=250$ μ s or $f=40$ pps, $T=300$ μ s. Stimulation current amplitude was adjusted continuously to the amplitude of the patient's tremor according to the control law of the device, which could implement a

passive or an active intervention. Gyroscope data were sampled at 50 Hz. The figure of merit adopted was the same as that used to quantify WOTAS effects on tremor.⁴⁷

Results

Figure 6 shows an example of the performance for both strategies. These examples correspond to wrist flexion-extension in a PD patient performing a postural task. We observe a remarkable attenuation in tremor for both interventions (middle and bottom plots) when compared with the monitoring mode. Tremor frequency is not altered in spite of the obvious proprioceptive information.⁴² Interestingly, the degree of attenuation does not vary with time once the system has passed through the transitory phase, which typically lasts ~ 1 s.

Figure 7 summarizes all the trials for the passive interventions of all the patients. More specifically, mean tremor reduction for passive intervention is $48.1 \pm 26.3\%$ (tremor attenuated in 44 out of 49 trials). The large standard deviation demonstrates that the response to this approach varies greatly, and this is mainly due to inter-subject differences. A more personalized selection of controller gains could overcome this problem. This was the case in four (out of five) repetitions in which passive intervention exacerbated the tremor.

Moreover, for passive intervention we observe a trend towards larger attenuation for more severe tremors, as was found for WOTAS (for a tremor power spectral density over $50 \text{ rad}^2 \text{ s}^{-3}$, attenuation becomes $22.8 \pm 21.3\%$).

We found a difference in attenuation between moderate and severe tremors with passive intervention (one-way ANOVA with repeated measures, $p=0.0471$; the two groups are made up of half of the trials with lower amplitude and half of the trials with higher amplitude).

This analysis focused on the wrist joint because the number of trials in which patients exhibited elbow tremor was very low.

Discussion

This paper described the concept of tremor suppression based on biomechanical loading. First, we introduced the WOTAS exoskeleton, which, although it was not deemed an acceptable solution for patients, demonstrated that the concept of biomechanical loading could be an alternative treatment for tremor. We also described the neuroprosthesis developed in the framework of the TREMOR project, which is based on the same principle but with a different technology (transcutaneous stimulation) in order to address the main limitations of the exoskeleton:

- 1) *Inefficient transmission of low forces through soft tissues.* The inconsistent suppression of moderate tremor was attributed to the attenuation of low external forces by soft tissues, which apparently prevented the application of the load on the skeletal system through external actuators mounted on mechanical structures.³⁸
- 2) *Improve the aesthetic, cosmetic, and usability aspects of the system.* In spite of the functional improvement perceived by patients, they were reluctant to use a bulky and unaesthetic device during daily living.^{38,43}

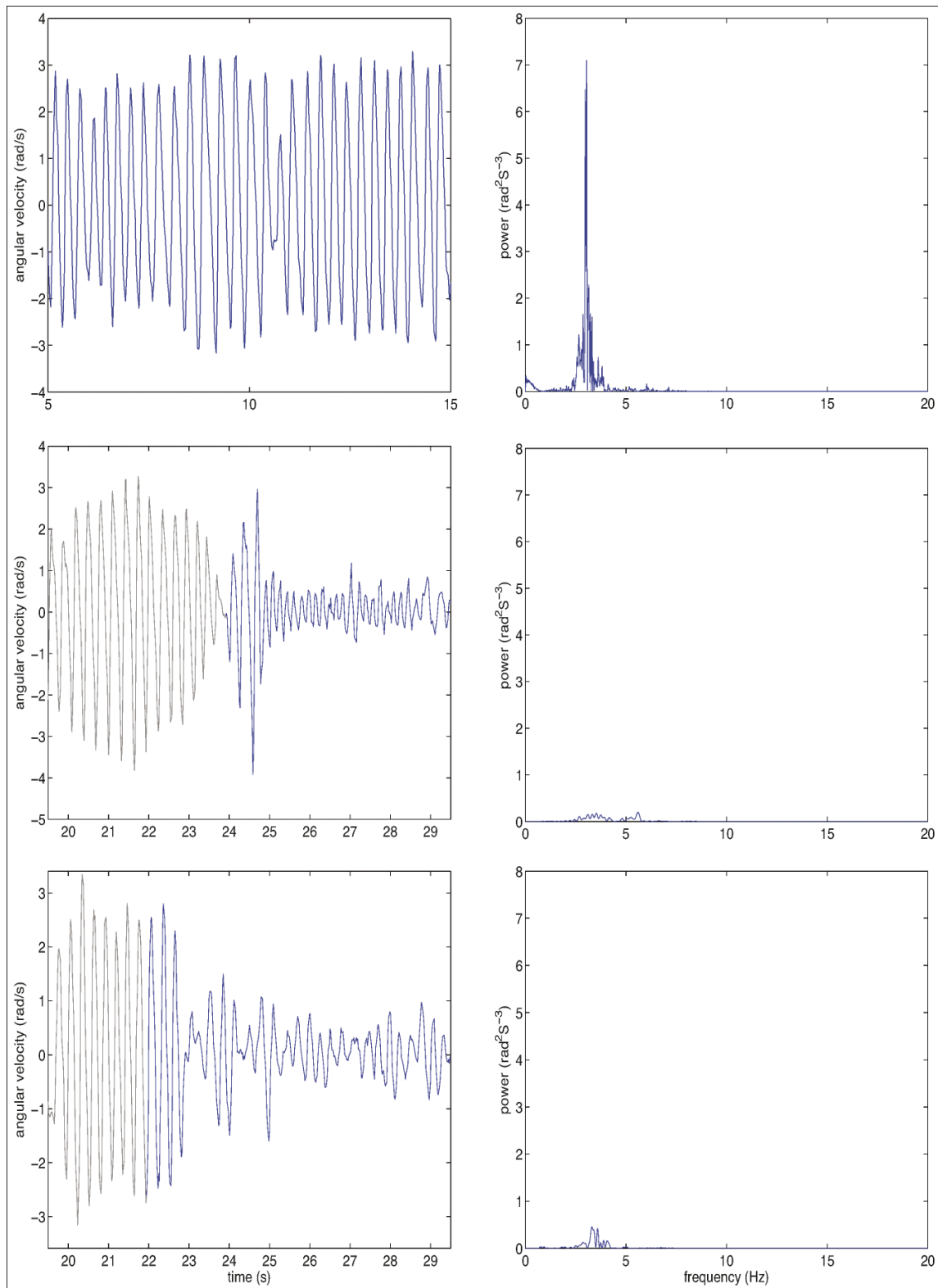


Figure 6. Example of the TREMOR Neurorobot in the Three Experimental Conditions (from top to bottom): Monitoring, Active, and Passive Modes. Left plots show wrist flexion-extension, and right plots show the associated power spectral density in a patient with Parkinson's disease. For the active and passive interventions, we show part of the trial without (gray) and with neurostimulation (blue). Remarkable tremor attenuation is obtained with both approaches.

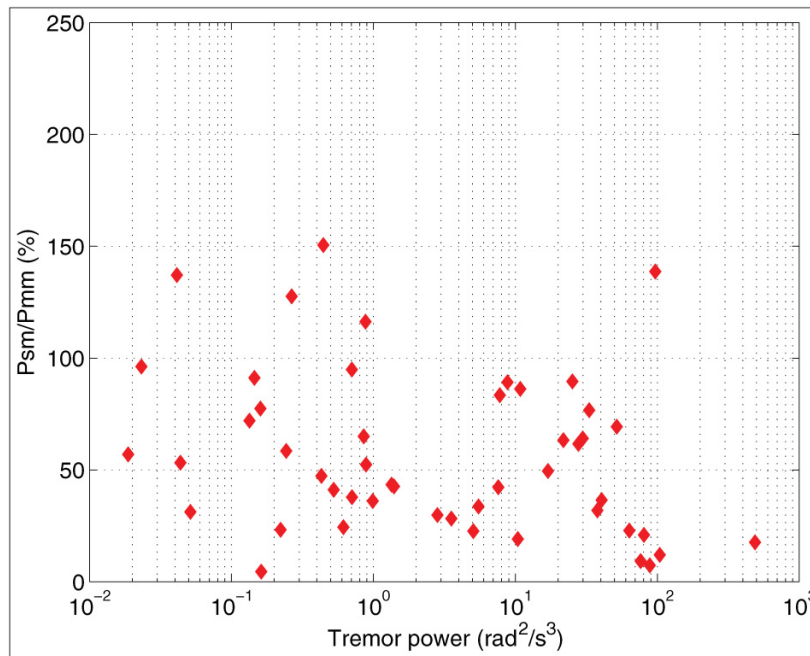


Figure 7. Tremor Reduction (Coordinate) Achieved by the TREMOR Neurorobot in Active (Blue) and Passive (Red) Interventions as a Function of Tremor Severity (Abscissa).

The results demonstrate that the approach effectively suppressed tremor in most of the patients. Importantly, this was independent of tremor type and etiology. The authors believe that this is because this approach acts on tremor manifestation. This is supported by the fact that neither approach altered tremor frequency despite obvious proprioceptive feedback. This is motivated by the central origin of parkinsonian⁷⁵ and essential tremor,⁷⁶ which predominates the other mechanisms that contribute to their genesis, mainly reflexes and mechanical oscillations.⁷⁷ Therefore, our results are in line with evidence for the limited role of sensory feedback in the generation, maintenance, and modulation of tremor in PD.⁷⁵ ET patients, however, exhibit a more evident interaction between the stretch reflex and the tremor itself,²⁵ the most noticeable example being the separation of both components, otherwise entrained, under inertial loading.²¹

Further research is required to 1) address the problem of tremor migration to more proximal joints (shoulder) where transcutaneous neurostimulation is not applicable; 2) improve neurostimulation capacity to control upper-limb movements, such as pronation-supination of the forearm; 3) evaluate the impact of tremor suppression on patient performance of daily activities; and 4) assess the accommodation of the patient to neurostimulation. These studies should be done in order to transfer this treatment to clinical practice.

The levels of stimulation used during the trials were below the levels used in clinical practice. The maximum current used with patients was perceived as acceptable, and none of the patients reported feeling pain. In summary, biomechanical loading is non-invasive and painless. It may be effective in patients who are insufficiently responsive (or have

adverse reactions) to drugs or in whom surgery is contraindicated. Moreover, this treatment avoids the potential side effects of drugs and the risks of surgical procedure.

The work presented here is based on clinical evidence with a limited number of patients (n=10 for WOTAS and n=12 for TREMOR), and most of them showed a positive response to the approach. Although the number of patients is small, it is considered sufficient to provide proof of concept of the feasibility and interest of using biomechanical loading as an alternative treatment for tremor. Owing to the reduced number of patients, the results of this study cannot be extrapolated to the general population and cannot be considered as clinical validation. Nevertheless, we are encouraged by the results and are considering the possibility of performing a large-scale multicenter validation of the TREMOR concept. We aim to include 500 patients (suffering from different pathologies that cause tremor) from 30–50 different hospitals around the world. The expected outcome is that biomechanical loading could either substitute or complement the pharmacotherapeutic management of tremors.

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