Design and Validation of a Neuroprosthesis for the Treatment of Upper Limb Tremor

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***Abstract*— Pathological tremor is the most prevalent movement disorder. In spite of the existence of various treatments for it, tremor poses a functional problem to a large proportion of patients. This paper presents the design and implementation of a novel neuroprosthesis for tremor management. The paper starts by reviewing a series of design criteria that were established after analyzing users needs and the expected functionality of the system. Then, it summarizes the design of the neuroprosthesis, which was built to meet the criteria defined previously. Experimental results with a representative group of 12 patients show that the neuroprosthesis provided significant ($p < 0.001$) and systematic tremor attenuation (in average 52.33 ± 25.48 %), and encourage its functional evaluation as a potential new treatment for tremor in a large cohort of patients.**

I. Introduction

Pathological tremor is the most prevalent movement disorder, affecting $\sim$ 15 % of people over 50 years according to some estimates [1]. It appears due to a number of syndromes yet not understood (see [2] for a review), being essential tremor (ET) and Parkinson's disease (PD) the most prevalent among them. Tremor is currently treated through drugs or neurosurgery, but unfortunately, it is not managed effectively in $\sim$25 % of the patients [3]. Thus, it constitutes a major cause of loss of independence and quality of life for many.

A number of alternative approaches for tremor management are reported in the literature (see [4] for a review). Among them, those devices based on the application of forces to the tremulous limbs show a considerable potential. These systems commonly rely on dissipative viscous elements (in a few cases combined with springs) to attenuate the tremor [5]–[13]. The rationale for this is that viscous elements exert a force that is proportional to velocity, and tremors are faster than volitional movements [14], therefore clinical and functional benefit should be, and in many cases is, obtained. The group of patients enrolled in the previous studies comprised the major tremor syndromes, except for PD, likely because these patients do not always exhibit intention tremor. From a design perspective, these systems span manipulanda [5], [6], [11], [15] and orthoses [7]–[10], [12], [13]. Orthoses may be classified, according to their implementation, as table-mounted [5]–[7], [11], [15], wheelchair-mounted [8], [15], or ambulatory-aimed devices [10], [12], [13]. The latter constitute the aim of our work, given that they have the highest potential to impact during the performance of activities of daily living (ADL).

An analysis of the drawbacks of ambulatory orthoses incorporating mechanical actuators yielded that soft tissues impede the efficient transmission of low forces to the musculoskeletal system, which hampers the implementation of solutions of this type [16]. Further, these type of orthoses are bulky, and thus not positively perceived by users [13].

This paper presents the design and validation of a neuroprosthesis (NP) for tremor management. The NP uses transcutaneous neurostimulation to compensate for the tremor, thus avoiding the need of external actuators. The system is conceived as a textile substrate that incorporates its main components, maximizing usability. The rationale for the application of force loads is the continuous modulation of muscle co-contraction according to the characteristics of the tremor. The results here presented provide evidence of clinical benefit, and encourage a large scale validation.

Partial results have been previously published in [17], [18].

II. Design of the Neuroprosthesis

This section presents the design criteria established for the cognitive and physical human-robot interfaces (cHRI and pHRI, respectively) of the NP, the major constituents of the system [19]. The concept is defined by taking into account both the characteristics of the population who will use the system (tremor patients, typically of advanced age), and the functional impact of tremor.

A. Concept Design of the Cognitive Human-Robot Interface

The goal of our NP is to provide a novel alternative for functional compensation of tremor during daily living. Hence, the NP is designed to actuate only when tremor may impede or hamper the realization of a voluntary movement. On the contrary, if tremor appears in a non functional context, like, for example, rest tremor in PD, the NP should not actuate. Further, the NP should be ideally triggered by the natural processes of the central nervous system, and not by "artificial" commands (or mental states [20]) that imply a learning process by the user, and thus are cognitively

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demanding. The use of natural commands has a strong positive impact on usability, and would permit expanding the use of the NP to the elder, and to people with mild cognitive impairment, as it is the case of many tremor patients [21]. These ideas are put together as a series of functional requirements for the cHRI, which is in charge of decoding user commands, and generating information to the pHRI that controls the NP [19]. These requirements are:

1) The NP must actuate only when it is needed, i.e. when the user wants to perform a volitional movement during which tremor may be cause of disability.
2) The interface must be natural, avoiding the performance of demanding cognitive processes.
3) The response of the interface must be fast, because some ADLs typically have short duration.
4) Tremor, in the presence of concomitant voluntary movement, needs to be accurately parameterized, ideally with no delay, in order to drive the controller that modulates neurostimulation.

The first two requirements imply that certain neural processes need to be detected and characterized, and impose the need of technologies that record the cortical structures that participate in movement planning and control. The third and fourth requirement, on the other hand, are also related to the signal processing techniques employed, and constrain their response time and accuracy respectively.

B. Concept Design of the Physical Human-Robot Interface

Upper limb tremor typically appears at the distal segments, being most prominent at the hands and the forearm for ET [22], and at the hands, commonly expressed as a "pill rolling" pattern (pronation-supination), for PD [23]. Functional analysis shows that wrist flexion-extension, forearm pronation-supination and elbow flexion-extension have the largest impact on disability [24], as expected from the segments exhibiting the most severe tremor. Moreover, given that the NP is envisioned as a functional compensation system, it has to suppress the tremor while not affecting the performance of volitional movements. Finally, for the prototype to be usable, neurostimulation has to be delivered in such a way that discomfort is avoided, and the appearance of muscle fatigue and accommodation delayed to the maximum. These ideas yield a series of requirements for the pHRI:

1) Tremor has to be attenuated at the degrees of freedom (DoF) in which it impairs the performance of ADLs.
2) The NP has to reduce tremor amplitude without affecting concomitant voluntary movement.
3) Drawbacks arising from neurostimulation, namely discomfort, appearance of muscle fatigue, and accommodation need to be avoided or minimized.

The first requirement is immediately met if the NP is capable of selectively activating the major pair of antagonists that control the movements defined above. Achievement of the second requirement needs for: *i*) the development of a control strategy that attenuates tremor but not voluntary movement, and *ii*) the selective activation of the targeted DoF(s), without affecting muscles that control other movements. The issues included in the third requirement are related to electrode placement, neurostimulation parameters, and their modulation.

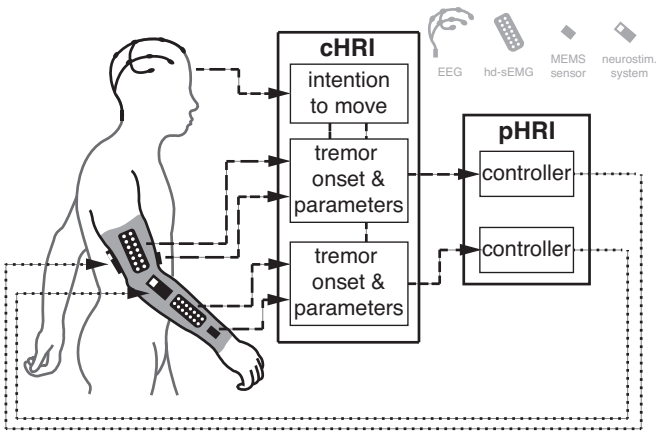

Fig. 1. Concept design of the NP, showing both the cHRI and the pHRI.

C. Implementation of the Neuroprosthesis

The cHRI implemented consisted in a multimodal interface comprising electroencephalography (EEG), surface electromyography (sEMG), and MEMS inertial sensors (solid state gyroscopes), and assessed the concurrent generation, transmission and execution of voluntary and tremulous movements (see Fig. 1). This interface triggered the NP when the user intended to perform a voluntary movement (as detected from the analysis of event related desynchronization with EEG [25]), and started the neurostimulation when volitional muscle activity was detected concurrently with the tremor (with sEMG). Then, it modulated the neurostimulation based on tremor parameters extracted with the solid state gyroscopes. This implementation met all the design criteria defined, namely, it was triggered in a natural manner to the user only when tremor appeared during a voluntary movement, and attained high accuracy and reliability with short delay (see [26] for details). However, due to the current lack of usablity of some of the technologies implemented (mainly the EEG), we decided to use a simplified cHRI that only included solid state gyroscopes for the validation. Thus, tremor parameters were estimated using the algorithm presented in [14], and fed into the controller at the pHRI.

Regarding the design of the pHRI, the NP stimulated the major pair of antagonists controlling wrist flexion-extension and elbow flexion-extention. However, muscles producing pronation are very deep [27], which renders accurate control of forearm pronation-supination with transcutaneous electrodes extremely complicated, and was thus disregarded. The last two design criteria were incorporated in the controller as follows. The control strategy we implemented relied on muscle co-contraction as a means to lower the natural cut off frequency of muscles ($\sim$2–3 Hz [28]), and attenuate the tremor. This approach inherently minimized the impact on voluntary movement, because it has lower frequency

than tremor [14]. Furthermore, the controller modulated continuously the amplitude of the current injected according to tremor parameters derived with the cHRI, therefore minimizing current density. This delayed to the maximum the appearance of muscle fatigue and the effects of accommodation to neurostimulation, and avoided discomfort. Thus, the pHRI fully met two of the three criteria previously defined, and one partly. Details on the controller are given in [18].

III. Methods

Twelve patients (2 female, mean ± SD age: 54.1 ± 17.5 years, from 22 to 70) suffering from PD (n = 3) or ET (n = 9) participated in the study. Tremor severity ranged from very mild to severe (from 2 to 30 according to Fahn-Tolosa-Marin score; rating only including the most affected limb). PD patients did not interrupt their medication for the recordings; ET patients were off medication for 24 h. All signed a written informed consent. The protocol was approved by the Ethical Committee at Universidad Politécnica de Valencia.

The NP comprised 4 solid state gyroscopes (Technaid S.L., Madrid, Spain), and 2 multichannel monopolar stimulators (UNA Systems, Belgrade, Serbia). It was implemented as a series of textile substrates that integrated the gyroscopes, and were placed over the stimulation electrodes. Patients wore the NP at the limb exhibiting the most severe tremor. Gyroscope placement followed [29]. Stimulation electrodes were located over the flexor carpi radialis, extensor carpi ulnaris, biceps (long head), and triceps (lateral head); common electrodes were placed at the wrist and the olecranon respectively.

Each patient performed a number of repetitions of two types of trials (named CO and NO). CO trials were divided into two parts: the first without co-contraction (NP off) and the second with co-contraction (NP on). With this design, we circumvented the possible influence of tremor fluctuations among trials. During the NO trials, the NP was never activated; the aim was to assess the natural variation of the tremor, and compare it with that caused by the NP in the CO trials. This way, we avoided that intra-trial tremor variations had an effect on the results. Trial duration was 30–35 s. The order of both types was randomized using latin squares. In total, each patient performed between 6 and 12 repetitions. When necessary, strategies to enhance the tremor were used (e.g. [30], [31]). During each trial, the patients performed the clinical task that made their tremor more evident. The task was chosen among the finger to nose test, the finger to finger test, resting the arm on the lap, and keeping both arms outstretched [22]. Controller gains and maximum stimulation amplitudes were identified manually before the recordings.

Tremor attenuation was computed as the ratio R_{att} of the integral of the power spectral density (p.s.d., 1 s windows, with zero padding) of the tremor during the part of the trial with neurostimulation, to the same variable without it (for CO trials) [13]. We also calculated R_{att} for the NO trials to investigate if the NP achieved a real tremor reduction (one-way ANOVA between the log-transformed CO and NO datasets). We present results only for the wrist, since many patients did not present persistent elbow tremor.

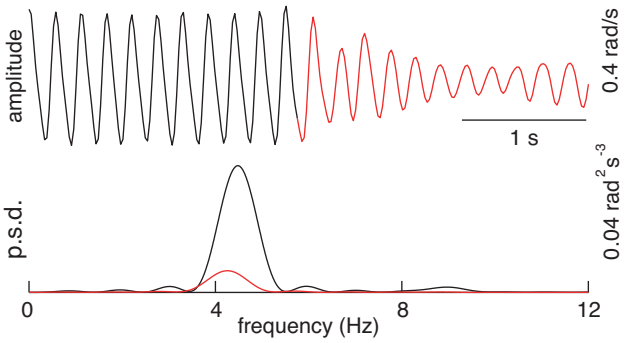

Fig. 2. Example of tremor suppression with the NP for an ET patient. Top plot: a small window of the data in the time domain; bottom plot: compares the p.s.d. without and with co-contraction in the entire trial.

TABLE I
Effect of the NP on tremor amplitude.

Pat.	Etiol.	Task	Freq. (Hz)	Ampl. NP Off (rad^{2}s^{-3})	Ampl. NP On (rad^{2}s^{-3})
01	ET	PO	4.24	111.60 ± 185.03	34.06 ± 26.59
02	PD	PO,RE	3.51	65.42 ± 41.31	35.80 ± 55.27
03	ET	PO,FN	5.11	15.68 ± 8.01	10.51 ± 4.10
04	PD	RE	4.81	0.80 ± 0.52	0.51 ± 0.23
05	ET	PO,RE	4.50	24.34 ± 42.86	2.37 ± 2.74
06	ET	PO	8.08	0.62 ± 0.09	0.21 ± 0.06
07	ET	PO	6.25	3.05 ± 2.76	1.08 ± 0.74
08	ET	PO	8.38	0.22 ± 0.05	0.17 ± 0.15
09	ET	PO	8.37	0.11 ± 0.08	0.01 ± 0.01
10	ET	FN	5.60	0.19 ± 0.08	0.12 ± 0.03
11	PD	PO	5.46	0.15	0.13
12	ET	PO	9.27	0.03 ± 0.01	0.02 ± 0.01

IV. Results

Fig. 2 presents a typical example of the performance of the NP, showing how the amplitude of the tremor was reduced after neurostimulation started. The data in the frequency domain illustrate that consistent reduction was obtained during the whole trial. Table I compares, for all patients and CO trials performed by each of them, the mean ± SD of tremor amplitude in the ensemble of periods without (NP Off) and with (NP On) co-contraction. Amplitude was quantified as the integral of the p.s.d.; tremor frequency was computed as the mean value in the absence of neurostimulation.

By grouping all trials with NP-driven tremor suppression (CO trials), we found that tremor amplitude was notably reduced (R_{att} = 52.33 ± 25.48 %) in 89.4 % of them (42 out of 47). This effect was statistically significant ($p < 0.001$, one-way ANOVA, see Fig. 3). The experimental design of the study, in which we compared the ratio R_{att} between the two periods of CO and NO trials, ensured that attenuation was not a natural effect of the tremor, but caused by the NP.

Our data suggested that more severe tremors were attenuated to a greater extent (e.g., tremor attenuation in trials with greatest amplitude before co-contraction was R_{att} = 22.8 ± 21.3 %), but the difference was not statistically significant (p = 0.083, Mann-Whitney test). A pooled analysis of tremor frequency without (NO trials) and with co-contraction (CO

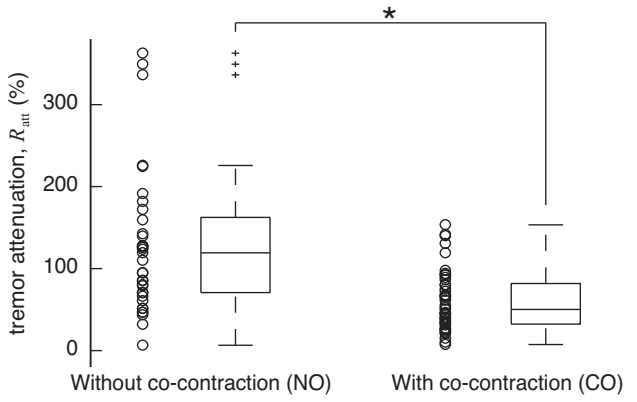

Fig. 3. Comparison of the variation of tremor amplitude within a trial, as measured by R_{att}, in the pooled datasets of trials without co-contraction (NO) and with co-contraction (CO). Each circle (○) represents a single trial in either condition. The box plots show the median (central mark), the first and third quartiles (upper and lower edges of the box), 1.5 times the interquartile range (whiskers), and the outsiders (+).

trials) demonstrated that the NP did not alter it (p = 0.808, one-way ANOVA), as expected from the central origin of ET and PD [2]. Tremor was not attenuated in 5 trials: *i*) in 3 of them two patients exhibited a tremor much milder than during calibration, and the NP did not elicit a contraction large enough because gains were underestimated, *ii*) in another, the patient's tremor was more severe than in previous trials, and the maximum stimulation amplitude limited too much the contraction level, and *iii*) in the last trial the patient exhibited accommodation to neurostimulation [32]. Adequate selection of controller gains and maximum stimulation amplitudes may have avoided these issues [18].

V. Conclusions

This paper provided a series of requirements that a wearable NP for functional compensation of tremor should meet. Based on them, we designed and implemented a prototype that was tested on a representative group of patients. The validation, which is presented here, demonstrates that the NP attenuated the tremor significantly and systematically in all the subjects, independently from its aetiology and characteristics, and encourages the functional evaluation of the system in a large cohort of patients.

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