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Mechanical suppression of essential tremor

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Abstract
This paper describes a new treatment for essential tremor. A wearable orthosis, which can be adapted to each configuration of each joint of the upper limb, is able to apply effective dynamic force between consecutive segments of the upper limb and change its biomechanical characteristics. The orthosis is controlled by a computer with a dedicated software application that distinguishes between real time tremor and voluntary movement. The wearable orthosis is able to detect position, rate and acceleration of rotation of the joint by means of a chip gyroscope. This technology was evaluated in six patients suffering from essential tremor. The technique is non invasive and represents an alternative to medication and deep brain stimulation.

Key words: *Essential tremor, human, muscle, side effects, robotics, viscosity*

Introduction

Essential tremor (ET) is defined by a bilateral postural tremor involving the upper limbs (1). A kinetic tremor, increasing in amplitude when the limb approaches a target, is often observed, and a head tremor may be associated. ET, a heterogeneous disorder, is the most common movement disorder in adults, with an estimated prevalence of 4% (2,3). Possible non-motor manifestations of ET, such as mood fluctuations or personality disorders, require further neuropsychological work assuming that they could share similar mechanisms with motor symptoms (4). Symptoms typically are progressive and disabling. The link between ET and Parkinson's disease is often a matter of debate (2).

The mechanism of ET remains to be elucidated (5). According to animal models of ET, an abnormal olivo-cerebellar activity would result in enhanced oscillatory activity in the cerebellum and its target nuclei in the thalamic circuits. However, recordings of neurons in human are not consistent with the theory of continuous olivo-cerebellar driving of the motor cortex via thalamic connections (5). ET might be induced by networks enabling tremor-related activity during voluntary movement and by enhanced access of sensory feedback. Given the role of the cerebellum in sensorimotor processing, a pathological coupling between sensory inputs and motor output may be considered (6,7). There is evidence from behavioural studies and imaging techniques that the cerebellar circuit is a plausible site for the genesis of ET. The clinical similarities between symptoms of ET and the symptoms in classical cerebellar disorders is obvious (1,8,9). Kinematic studies are highly suggestive of a genuine cerebellar disorder, and magnetic resonance spectroscopy reveals decreased N-acetylaspartate/creatine ratios (NAA/Cr) and N-acetylaspartate/choline ratios NAA/Cho ratios in the cerebellum of ET patients, indicating a possible degenerative phenomenon with neuronal dysfunction (10,11). An inverse association between cerebellar cortical NAA/Cr ratios and arm tremor severity has been observed. The favourable effect of ethanol reported in ET could be due to an effect on neuronal activity of inferior olivary cells or an effect on alcohol-sensitive GABA receptors within the cerebellum (10,12). Ethanol administration decreases complex spikes and increases simple spike activity generated in the inferior olive.

Current treatments of ET include drugs (mainly primidone and propranolol), and surgery (thalamotomy and deep brain stimulation) in patients refractory to medications, in which the response is considered insufficient or only partial (3,13). However, (a) ET is not managed effectively or sufficiently in about 25% of patients, (b) the drugs

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used often induce side effects or may be contraindicated, and (c) surgery is associated with a risk of hemorrhage and psychiatric manifestations (14). In particular, a high rate of suicide (4.3%) has been observed recently in patients treated with deep brain stimulation (15). Paradoxically though, patients developing psychiatric symptoms often experience significant motor improvement following a surgical procedure (15). Therefore, further research and new therapeutic options are required to manage ET more effectively. It has been established in the literature that essential tremor responds to biomechanical loading. In particular, it has been clinically tested that the increases of damping and/or inertia in the upper limb leads to a reduction of the tremorous motion, i.e., the change in impedance characteristics of the upper limb has a direct effect on the tremor characteristics (16,17). This phenomenon gives rise to the possibility of an orthotic management of tremor. Biomechanical loading for tremor reduction can be approached either by ambulatory robotics based orthotic devices or by non-ambulatory table or wheelchair mounted devices. The former approach is characterized by selective tremor suppression through internal forces at particular joints, while the later relies on global application of external forces that leads to the overall tremor reduction. While wearable tremor suppression exoskeletons are already a matter of research, non-ambulatory systems have lead to commercial products, see, for instance, the so-called Neater Eater (18). In addition, the MIT damped joystick (19), the controlled Energy-Dissipation Orthosis, CEDO (20), or the Modulated Energy Dissipation Arm, MED, [cited in 21], are implementations of non-ambulatory, wheelchair-mounted tremor suppression prototypes. As far as wearable tremor suppression concepts are concerned only the well-known wearable tremor-suppression orthosis (21) has been reported in the literature. This is a passive damping loading device, which acts mechanically in parallel to the wrist in flexion-extension. It completely constrains both wrist abduction-adduction and prono-supination.

This paper discusses the effects of a new therapeutic strategy based on biomechanical loading of the tremor in six patients exhibiting a definite essential tremor (1). Biomechanical loading of tremor was achieved through a robotic wearable device called WOTAS (Wearable Orthosis for Tremor Assessment and Suppression), which acts in parallel to the affected limb and is able to apply damping or inertial load to a selected set of limb articulations. Innovations of this technique are: (i) the orthosis ability to apply forces between segments of the upper limb, and (ii) the intelligent detection of tremor vs. voluntary motion, in such a way that the orthosis does not load the voluntary movement of the patient.

WOTAS will be briefly described in the following section. This will be followed by the presentation of the materials and methods used during the clinical trials. Next, the results obtained are presented. Finally, the discussion and the conclusions of this study are given.

Description of the technique

The active orthosis (exoskeleton) WOTAS was developed under the framework of the European project DRIFTS (22). The concept of WOTAS is to develop an active upper limb exoskeleton based on robotic technologies capable of applying forces to cancel tremor and retrieve kinematic information from the tremorous upper limb. This active orthosis is equipped with kinematics (angular position, velocity and acceleration) and kinetic (interaction force between limb and orthosis) sensors. The WOTAS active orthosis has built-in gyroscopes (ENC-03J manufactured by Murata Inc.) for tremor measurement in each of the controlled joints. Moreover, it could also apply dynamic force to the articulations of the upper limb by means of a set of flat brushless DC motors + pancake gears (23) selected to be a compact and light weight solution suitable for a wearable device. The orthosis is adaptable to each configuration of the joint between different patients owing to the use of thermoplastics. This robotic device spans the elbow and wrist joints, being able to apply independent tremor suppression strategies to elbow flexion-extension, wrist flexion-extension and wrist pronation-supination, see Figure 1. The total weight of the final system is roughly 850 g. Innovations of the WOTAS exoskeleton are the following: its portability, it is a non invasive system, and provides direct information from each joint of the upper limb, allowing the estimation of the contribution of each joint to the

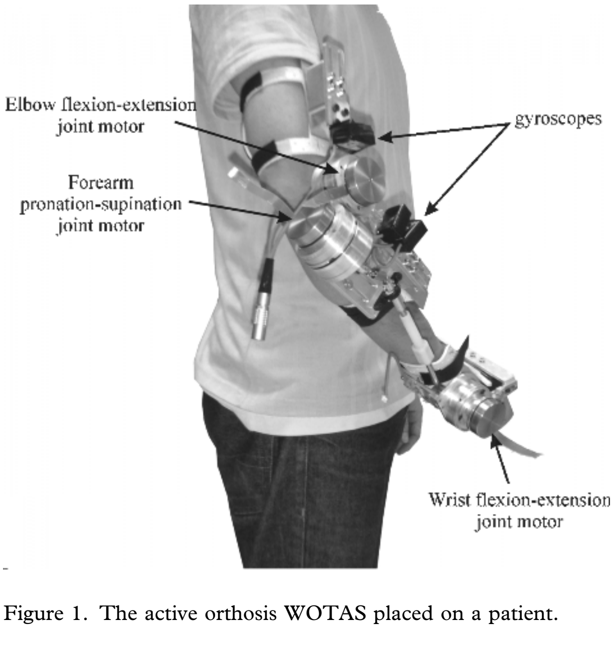

Figure 1. The active orthosis WOTAS placed on a patient.

overall tremorous motion in the kinematic chain of the upper limb.

WOTAS' control architecture is mainly composed of three elements, namely, the exoskeleton structure with its sensors and actuators; a microprocessor which executes the real-time control algorithms of the orthosis and a standard desktop PC that works as a host computer and implements the interface with the clinician. The active orthosis is controlled by a computer with a dedicated software application that implements an algorithm able to distinguish *in real time* tremorous from voluntary movement and to calculate the force applied by the active orthosis over the upper limb in order to change its biomechanical characteristics and, consequently, suppress tremor.

The algorithm developed for the WOTAS orthosis is based on a two-stage method that estimates voluntary and tremorous motion in real-time (23). After a comparison between several tracking algorithms (23), the Benedict-Bordner filter was selected for the estimation of voluntary motion. The estimated voluntary movement is removed from the overall movement and the resulting movement is supposed to be the tremorous movement. After this, we use the Weighted-Frequency Fourier Linear Combiner (WFLC) in order to estimate tremor parameters. The WFLC is an adaptive algorithm that estimates tremor using a sinusoidal model, estimating its time-varying frequency, amplitude and phase (17). The filtering on the first stage is implemented in order to estimate and use filter equations to distinguish tremorous from overall motion with reduced phase lag, but without considering high frequency movements (such as tremors). The second filtering stage estimates both the amplitude and frequency of the tremorous movement on the assuming that the remaining movement from stage one is not voluntary. Experimental results with 33 subjects presenting different tremor diseases showed that the algorithm is capable of estimating in real-time (roughly 1 ms of time delay introduced) the voluntary and tremor components from the overall movement.

Material and methods

Patients

All patients were right-handed (Mean age 72.3 years; Females: 3; Males: 3). ET was moderate in patients 1, 3, and 4 and severe in patients 2, 5, and 6. Patients were still exhibiting a bilateral postural tremor in upper limbs despite regular intake of medication (mysoline, propranolol or a combination of both at usual doses for ET). The protocol of the experiments was informed to the patients before the trials and signed-up an informed consent. The investigation was approved by the ethical committee of Hôpital Erasme-ULB, Bruxelles (ULB).

Protocol

Three different people were present during the measurements:

(1) A computer operator for setting the parameters of the system and recording the signals.
(2) A clinician for supervision of the condition of the trials and the state of the patient.
(3) An experimenter to aid the patient don and doff the orthoses and interact with them to perform the trials.

The active orthosis WOTAS is able to operate in two different modes: the *suppression* mode in which the system is able to simulate different parameters of viscosity and inertia to the joints of the upper limb and the *monitoring* mode in which WOTAS operates in free mode (no force is applied to the upper limb) and monitors tremor parameters of the patients. During the experiments neither the patient nor the experimenters knew when the system was applying a suppressing strategy or when it was operating in *monitoring* mode. Only the computer operator knew when the systems were applying the suppression strategy. This experimental design was used to reduce the placebo effect in the experimentation. All the experiments were recorded on video.

Tasks

Three different tasks were selected: keep the upper limbs outstretched, point to the nose with a finger, and keep the arm in a rest position. These tasks have been previously used to characterize tremor movement (24). These tasks were selected:

(1) To have a representation of the different forms of tremor (24).
(2) To cover tasks that can be meaningful from the point of view of function. For this second issue, a good correlation was found (25) between these tasks and the functional scale for the assessment of tremor severity (Tolosa and Fahn's scale) (33)

The experiments were balanced to avoid interactions in the analysis, as well as learning effects (25). The order in which the modes were applied was alternated, as well as the order in which the patients executed the tasks. In each experimental session, 3 repetitions of each task were realized. The number of repetitions was chosen to have an experimental session not longer than 1 h.

Data analysis

The data analysed were the output voltage coming from the gyroscopes placed on the active orthosis.

The figure of merit adopted to quantify the reduction achieved by the active orthosis is the ratio between the signal analysed in *monitoring* mode (P_{mm}), and the signal analysed in *suppression* mode (P_{sm}). Therefore, the reduction of tremor was measured with the patients under the same conditions: with the orthosis placed on the upper limb. As a result, the reduction estimated is the remaining tremor in *suppression* mode referred as a percentage of the tremor with respect to the *monitoring* mode.

Results

The effects of adding effective viscosity were investigated for the upper limb during the execution of the different clinical tasks. During the trials, some patients were able to identify when the system was operating in *suppression* mode, relating to the clinician 'now the system is suppressing my tremor', and 'now it is not'.

Figure 2 illustrates the performance of WOTAS when operating in *suppression* mode showing the efficiency of the active orthosis increases as tremor power increases. This shows a lower limit for efficient tremor suppression, this limit is roughly 0.16 $(rad/s)^2/Hz$. These lower limits for tremor suppression should be determined by the physical interaction between the orthosis and the upper limb. This physical interaction is bidirectional: on the one hand, the orthosis must transmit the loads to the bones for tremor suppression. This transmission is mediated by the soft tissues between the supports and the actuator. Usually, the effect of load transmission is negligible in common orthotics. However, tremor has a pure dynamic component. Therefore the characteristics of the transmissions through the soft tissues play an important role in the efficiency of tremor suppression. On the other hand, the orthosis should be able to measure tremor activity. This process is also affected by the transmission of movements from the upper limb to the orthosis since this transmission is also performed through soft tissues. Both factors are more crucial for lower amplitude tremors. These results indicate that there is a physical limitation for tremor suppression through wearable devices due to force transmission through soft tissues.

According to the results, the range of tremor suppression of the signals above this orthosis operational limit ranges from 2.9% (percentile 5) to 78.5% (percentile 95) in relation to energy in the *monitoring* mode. The results also indicated that the device could achieve a consistent 40% of tremor power reduction.

Figure 3 illustrates the effects of WOTAS in the tremorous movement when operating in *suppression* mode. Figure 3 (upper traces) shows the time series corresponding to the tremorous movement of the wrist joint during the arm outstretched task of patient 2. The top left part of the figure shows the time signal with WOTAS in the *monitoring* mode. The top right part illustrates the time series when the orthosis is operating in *suppression* mode. Notice that the amplitude of tremor is clearly lower than in the *monitoring* mode.

Figure 3 (bottom) shows the representation of the Power Spectrum Density of the same time series represented on the upper panels. The PSD was obtained from the part of the signal with tremor. The left part of the figure illustrates the PSD of the tremorous movement with WOTAS operating in *monitoring* mode. It is possible to see a clear peak of tremor activity close to 6 Hz. In the right part of the figure the peak of energy corresponding to the tremorous activity when WOTAS is operating in *suppression* mode presents a clear reduction. The

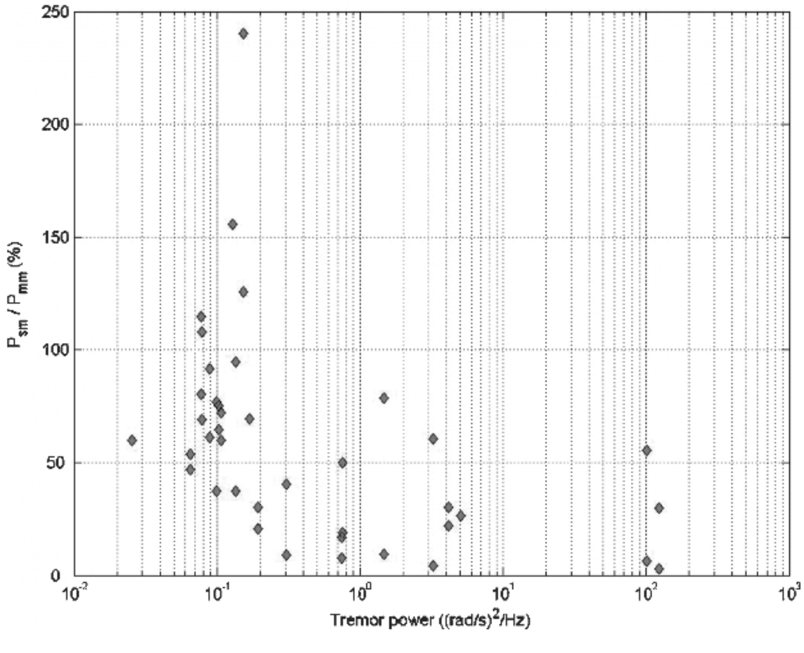

Figure 2. Tremor reduction achieved by WOTAS.

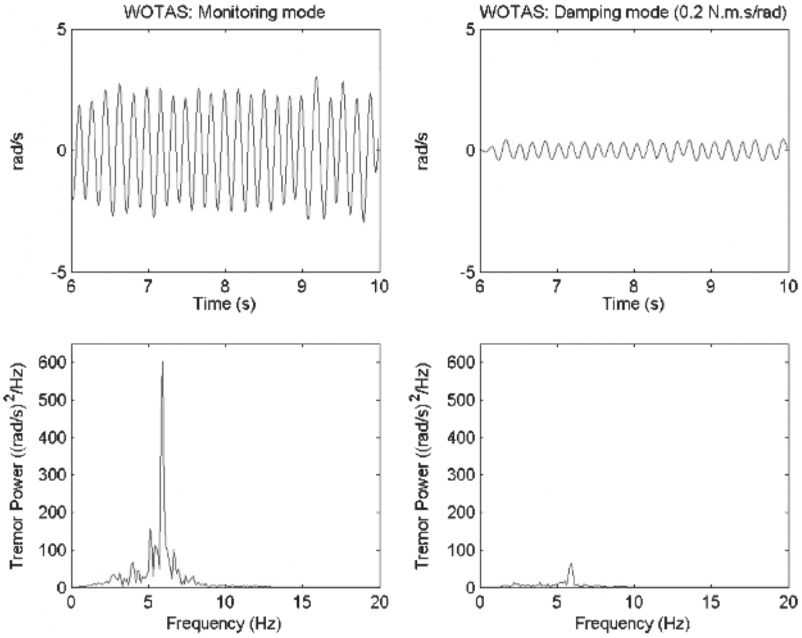

Figure 3. This figure illustrates the oscillations of the elbow and the associated power spectral density (PSD) of tremor with the motor in a free mode (left panels) and providing viscosity of 0.2 Nms/rad (right panels) in patient 2. Note the strong reduction in the PSD when viscosity is applied. The tremor is detected by a chip gyroscope fixed on a metallic bar. Oscillations are expressed in rad/sec and PSD is expressed in $(\text{rad/s})^2/\text{Hz}$. The solution used to actuate the orthosis is a combination of a flat brushless DC motor and a pancake gear. Brushless servo motors have electronic commutators, isolated from high bus voltages. As a result, higher speeds and torques can be achieved. The motor is controlled in real time. Output voltage from the gyroscopes processed at 2000 Hz. Data filtering: Kernel smoothing algorithm. Duration of acquisition: 30 sec.

reduction of the power spectral density (PSD) was 80.4% in this patient. Results indicate that reductions of tremor can be as high as 98% for severe cases of tremor. In addition, the analysis of the video record indicated that in the majority of patients there was no displacement of tremor movement to proximal joints. Nevertheless the authors believe that it is important to investigate and define the profile of the users affected by this new phenomenon.

There are suggestions that the mechanical suppression of tremor could produce a positive feedback to essential tremor patients. Patients reported that when they realized that the orthosis was suppressing tremor they felt a reduction in the tremor itself and felt more confident to accomplish the task. This behaviour has been detected in patients with severe tremor and requires further research to be confirmed.

During the trials, patients reported that the orthosis does not limit their range of motion. In addition, no patient felt that the orthosis applied loads on their voluntary movement. Patient tolerance was good. No lesions were observed on their skin, except for a moderate and transient change in skin aspect due to the orthosis. Slight discomfort was reported by some patients. These results suggest this new technique is a possible therapy for tremor suppression in humans.

The patients considered that the use of such a device could cause social exclusion. This was expected since the exoskeleton was developed as a platform to evaluate the concept of mechanical tremor suppression and not as a final orthotic solution.

Discussion and conclusions

This paper reports a new solution for tremor suppression in humans using an active orthosis simulating viscosity. The adaptive viscous control method is non invasive. It may be effective in patients who are insufficiently responsive (or have adverse reactions) to drugs or in whom surgery is counter-indicated. This technique avoids the potential side effects of drugs and the risks of surgical procedure. Although deep brain stimulation has provided remarkable benefits for people with a variety of neurological conditions (26), alternative solutions are of interest for refractory cases. From the motor control point of view, deep brain stimulation has also the disadvantage of impairing the adaptative control of reaching (27). In ET patients with electrodes placed in the cerebellar thalamus, the larger the stimulation voltage the greater the reduction in rates of adaptation. In patients with unilateral thalamotomy, the adaptation in the contralateral arm is also impaired as compared to the ipsilateral arm (27). Therefore, although both central neurostimulation and lesions are very effective to manage tremor, both techniques significantly impair the capacity of the brain to form internal models of action (27–31). Indeed, the adaptative control of reaching depends on the integrity of the cerebellothalamocortical pathway.

Oscillations occur frequently in biological systems (32). Interactions with the environment induce tremors in the human body. The mechanical properties of the neuromuscular system and the effects of reflexes explain the features of these involuntary movements. Because muscles can be compared to viscoelastic structures, they are involved in damping, the dissipation of mechanical energy. Potentially, reflexes can modulate the relative magnitudes of the viscous and elastic components of the mechanical impedance provided by muscle (32). The technique described here may be seen as an adaptive device which cancels oscillations of tremor by governing and re-directing the movement at the effector level. The potential compensatory mechanisms which might occur in the central nervous system in the mid- or long-term remain to be defined.

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