Artificial Organs

On the Use of Fixed-Intensity Functional Electrical Stimulation for Attenuating Essential Tremor

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Abstract: A great proportion of essential tremor (ET) patients have not so far been able to receive functional benefits from traditional therapies. In this regard, the use of functional electrical stimulation (FES) has been proposed for reducing tremor amplitude by stimulating muscles in antiphase with respect to the trembling motion. Although some studies have reported success in terms of tremor attenuation, drawbacks still exist that prevent the method from being used in real-life applications. In this article, we explore an alternative approach: a strategy based on the hypothesis that FES-induced constant muscle contraction may provide functional benefit for tremor patients. To evaluate the proposed strategy, experiments were conducted in which stimulation was intermittently turned on and off while the subjects performed a static motor task. The results of the proposed experimental protocol indicate that tremor attenuation using this strategy is feasible, as consistent tremor attenuation levels were obtained in eight out of 10 ET patients. Nonetheless, tremor reduction was not instantaneous for all successful trials, indicating that prior training with FES may improve the overall response. Furthermore, although simpler assistive devices may potentially be designed based on this technique, some experimental difficulties still exist, which suggests that further studies are necessary.
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Tremor, which involves involuntary, approximately periodic, and roughly sinusoidal movement, is one of the most common movement disorders (1). In particular, essential tremor (ET) is a monosymptomatic pathology whose patients usually present postural tremor aggravated by voluntary movement, which thus considerably decreases their ability to perform simple daily tasks. Currently, the main available treatments for ET are based either on drugs or on invasive interventions such as deep brain stimulation (DBS). However, drugs lack effectiveness, with positive outcomes for many patients being limited, while invasive interventions are still costly and may produce side effects (2).

In order to enable the development of new therapies, a suitable approach would be to investigate the inner dynamics of pathological tremor, as was done by Zhang and colleagues (3), including the relation between central oscillators and peripheral mechanisms in the origin of ET. However, to our knowledge no results have been obtained using this methodology so far, and hence alternative treatments based on the use of assistive technology have been proposed. One example of such a device is the active upper-limb exoskeleton (4), an orthosis that is directly coupled to the joints and actuated in order to counteract tremor. This system presented satisfactory performance in preliminary trials; nevertheless, its unwieldiness hampers its practical use in daily life.

In order to directly actuate the tremulous joints concerned, an option would be to apply functional electrical stimulation (FES). FES is based on the principle of delivering electric pulses to the muscle to produce contraction, either to move the limb or to modulate the joint impedance by co-contraction (5). Compared with active orthoses, FES systems are potentially lighter and smaller, and there is no need to adjust the device for different users. However, in spite of its potential for different applications, practical use of FES still presents significant challenges (6), particularly when superficial electrodes are used.

From an engineering perspective, such FES systems must contain sensors that detect or estimate the features of the tremor as they vary with time. Based on this information, stimulation parameters can be modulated in real time to reduce tremor while minimizing interference with voluntary motion. In a previous article (7), we targeted the problem of tremor estimation in real time. The current article concerns FES actuation strategies to adequately attenuate the effects of pathological tremor.

Pioneer studies on the topic (8), and also more recent studies (9,10), were based on applying FES to activate antagonist muscles in antiphase with respect to the trembling motion in order to reduce tremor amplitude. Using this strategy, it has been demonstrated experimentally that tremor attenuation using FES is feasible. Moreover, in some cases the positive effect was instantaneous and enduring. Nevertheless, certain drawbacks of the method have come to light that still prevent current use in daily life by patients. First, these methods rely on FES-induced motion, which is a great obstacle to daily use due to difficulties concerning electrode placement and because the muscles activated by surface electrodes change during forearm motion (i.e., for different forearm orientations, the same electrodes may be stimulating different muscle groups). Also, increase in tremor amplitude may occur due to errors in tremor phase estimation or in controller parameters, which may be aggravated if manual tuning of parameters before each use is required (8). Lastly, greater discomfort, caused by variation in stimulation intensity with time, was felt by some patients.

An alternative to antiphase stimulation is based on the idea of increasing the affected joint's impedance using electrical stimulation and thereby reducing tremor amplitude. The approach is inspired by strategies often employed by tremor patients in daily life, such as coactivating the muscles to amplify joint impedance and supporting the tremulous limb against a fixed object, such as a table, or holding it with the unaffected hand. In terms of musculoskeletal dynamics, increasing joint impedance without producing any residual joint motion is possible when antagonist muscles deliver equal but opposing torques to the joint. In this condition, joint impedance may be modulated by the muscles' activation level due to both intrinsic and proprioceptive contributions to the active viscoelasticity of the muscles (11).

Preliminary evaluation of this approach, indicating good results, has already been performed in simulation (12), on healthy subjects (13), and in tremor patients (14). It is a promising approach as the constant low-level stimulation applied might be more comfortable and produce less fatigue. Furthermore, the resulting portable device may be simpler, which is an important advantage considering that tremor often propagates from proximal to distal joints. Nonetheless, in the previously cited works, a closed-loop system that modulated the FES level based on the estimated tremor intensity was used. For that reason, the stimulation applied varied with time due to the closed-loop system dynamics, possibly preventing precise understanding and, more importantly, quantification of the phenomenon that produced actual tremor attenuation.

In view of this situation, in this article we propose a new experimental protocol for evaluating FES tremor attenuation, in which fixed-intensity FES is applied to muscles acting on the tremulous joint while a static task is performed. By maintaining the maximum number of variables at fixed levels, we expect to obtain accurate information on how this complex pathological motion may be compensated for. Also, as the ultimate goal is not to completely suppress tremor, but instead to provide the greatest functional benefit, the proposed scheme may present the additional advantage of enabling the subject to easily adapt his/her motion patterns, as FES intensity is constant.

In order to perform a preliminary evaluation of the method, experiments with 10 ET patients were conducted. The trials featured an initial tremor characterization, where the muscles to be stimulated were chosen, and subsequent static tests using an open-loop FES system. As the protocol was based on single-session experiments, patients could not provide an evaluation of functional benefit obtained in daily use. However, tremor amplitude attenuation could be quantified based on the obtained data, and the feasibility of the approach was demonstrated. Furthermore, the obtained data illustrated heterogeneous phenomena; hence, in this article we are also focused on discussing their possible causes and the potential advantages of this method compared with alternative methods.

PATIENTS AND METHODS

Participants

A group of 10 ET patients participated in the study. In Table 1, information concerning the participants is given. The subjects were selected randomly from patients at the Centre Hospitalier Universitaire de Montpellier, and they presented heterogeneous tremor features in terms of both age at tremor onset and tremor severity according to the Fahn–Tolosa–Marin tremor rating scale. None of the patients had experienced surface electrical stimulation beforehand. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee, and all participants signed informed consent forms.

Design

The study used a within-subject design to evaluate the feasibility of the proposed method. The experiments were limited to a single session where participants were given a static motor task to perform. The relative tremor amplitude was measured during alternating periods when fixed-intensity FES applied to the wrist or fingers was turned on or off.

Materials

The experimental setup consisted of a commercial stimulator, the Cefar Physio 4 (Cefar, Malmö, Sweden), and motion-sensing units composed of a three-axis accelerometer (MMA7260Q, Freescale, Austin, TX, USA) and a two-axis gyrometer (IDG300, Invensense, San Jose, CA, USA) sampled at 100 Hz. The sensor box was placed using fastening tape either on the fingers or on the hand, depending on the tremulous joint. In our setup, the x-axis was pointing distally, the y-axis medially, and the z-axis anteriorly. Self-adhesive round electrodes 3.2 cm in diameter were used in the experiment. For smaller muscles in the forearm, smaller electrodes were used to provide better selectivity. As the stimulation intensity was set manually, we also used electromyography (Biovision, Wehrheim, Germany) coupled with the inertial sensor acquisition system. Based on the corresponding stimulation artifact, we could guarantee precise synchronization between FES and motion signals recorded using inertial sensors.

Procedure

First, the pathological motion was analyzed using inertial sensors in order to designate the appropriate target joint(s) for stimulation (wrist, fingers, or thumb/index), as well as the muscles concerned. The joint presenting higher tremor amplitude, considering that tremor propagates from proximal to distal joints, was selected. Once these definitions were made, FES parameters were set for each muscle individually while the participants were performing a static motor task: pointing to a target with the hand, maintaining the arm in full extension. Furthermore, the limb was not constrained in any possible degree of freedom (DOF). FES pulse width was fixed at 150 μs and frequency at 40 Hz, while stimulation level was regulated manually using pulse amplitude (mA) based on visual and tactile inspection of muscle contraction but respecting patients' subjective evaluation of discomfort. The main goal for setting the stimulation parameters was to produce consistent isometric contraction while avoiding reaching the motion threshold. As multiple muscles may affect joint motion, within the initial setup different candidate muscles were stimulated, and the muscles that presented the best response based on visual inspection were selected for evaluation.

Following the initial setup, evaluation was based on the intermittent application of constant levels of stimulation. Stimulation duration was incremented progressively from approximately 10 s up to 50 s to enable evaluation of different effects that may affect

TABLE 1. *Descriptive data on all patients who participated in the study*

Patient	Gender	Age	Age at onset	Tremor severity*
A	M	54	10	2
B	F	78	15	3
C	M	71	56	2
D	M	57	6	3
E	M	77	10	2
F	M	75	73	3
G	M	76	32	4
H	M	71	1	2
I	M	79	20	4
J	F	65	60	2

* Postural tremor of the dominant arm, measured on the Fahn–Tolosa–Marin rating scale; more severe tremors are represented by higher values.

TABLE 2. *Data resulting from the experiments*

Patient	Target joint	Stimulated muscle(s)*	Most significant tremor attenuation (%)*	Overall response
A	Fingers	FDS	−65.49†	No positive effect
B	Wrist	FCU, ECU	12.53	
C	Fingers	EDC, FDS, PT	94.68	Attenuation preceded by an adaptation phase
D	Fingers	FCR	78.20	
E	Thumb/index	AP, APB	72.07	
F	Wrist	ECU, FCU	85.69	Clear, immediate attenuation
G	Wrist	PT	41.73	
H	Wrist	EDC	37.18	
I	Fingers	EDC	47.28	
J	Thumb/index	AP, APB	78.19	

* Reduction in tremor amplitude on the sensor axis presenting highest tremor intensity before stimulation.
† The minus sign indicates that performance was worse when FES was on.
FDS, flexor digitorum superficialis; FCU, flexor carpi ulnaris; ECU, extensor carpi ulnaris; EDC, extensor digitorum communis; PT, pronator teres; FCR, flexor carpi radialis; AP, adductor pollicis; APB, abductor pollicis brevis.

tremor attenuation. Periods in which FES was turned off lasted for at least 10 s, while longer intervals were employed when subjects were not able to reestablish static hand position immediately after stimulation. A sequence of five to seven stimulation periods was applied during each session. Before the stimulation trials started, the patients initiated the static task and remained in this position for at least 10 s in order to minimize transient effects. If requested by the subject, resting periods were allowed between stimulation periods to limit overall muscle fatigue. Furthermore, it was not possible in any stimulation trial to start stimulation directly at the assigned intensity. Instead, due to the limitations of the employed stimulator, current amplitude was increased until the target level was achieved, in a procedure that took approximately 5 s to complete. During the whole session, upper limb motion was measured using accelerometers and gyrometers.

Afterward, the resultant recorded motion was analyzed to enable comparison of tremor amplitude with and without FES and identify other effects that emerged. The data used in the analysis were preprocessed (high-pass 10th-order Butterworth filter, cutoff frequency at 1 Hz) to remove low-frequency components. Considering the tasks performed were static, the filtering was applied mainly to remove sensor bias from the signal.

RESULTS

The results obtained in the study are summarized in Table 2 and Figs. 1 and 2. In addition to the quantitative data related to tremor attenuation experiments, Table 2 also includes information concerning the target joint and the stimulated muscles, as well as a classification of the overall response to FES therapy into three categories: no positive effect; attenuation preceded by an adaptation phase; and clear, immediate attenuation. Tremor amplitude was computed using the root mean square (RMS) value of the relevant motion signal, while tremor attenuation was defined by the ratio

$$\frac{RMS_{off} - RMS_{on}}{RMS_{off}} \tag{1}$$

where "on" and "off" refer to all periods in which stimulation was on and off, respectively. The results concerning the overall response to FES were obtained directly by analyzing the acquired motion signals, particularly the transient response when FES was turned on and off.

The results in Table 2 illustrate the overall success of the method, particularly as the trials resulted in increasing tremor amplitude in only one out of 10 patients, and tremor attenuation was lower than 37% in only one out of nine patients.

The general performance of the method for all patients is also illustrated in Fig. 1. Data from all sensors and the corresponding mean tremor amplitude (represented by its RMS value) for the periods in which FES was on and off are shown. As fixed-level stimulation may displace the joint and affect the plane of motion of the tremor as a result, evaluating all measured axes is important to verify if the tremor has shifted to a different plane, which would prevent effective functional benefit to the user.

Finally, in order to illustrate motion response with respect to time, pieces of data that contain representative effects are depicted in Fig. 2 to substantiate the

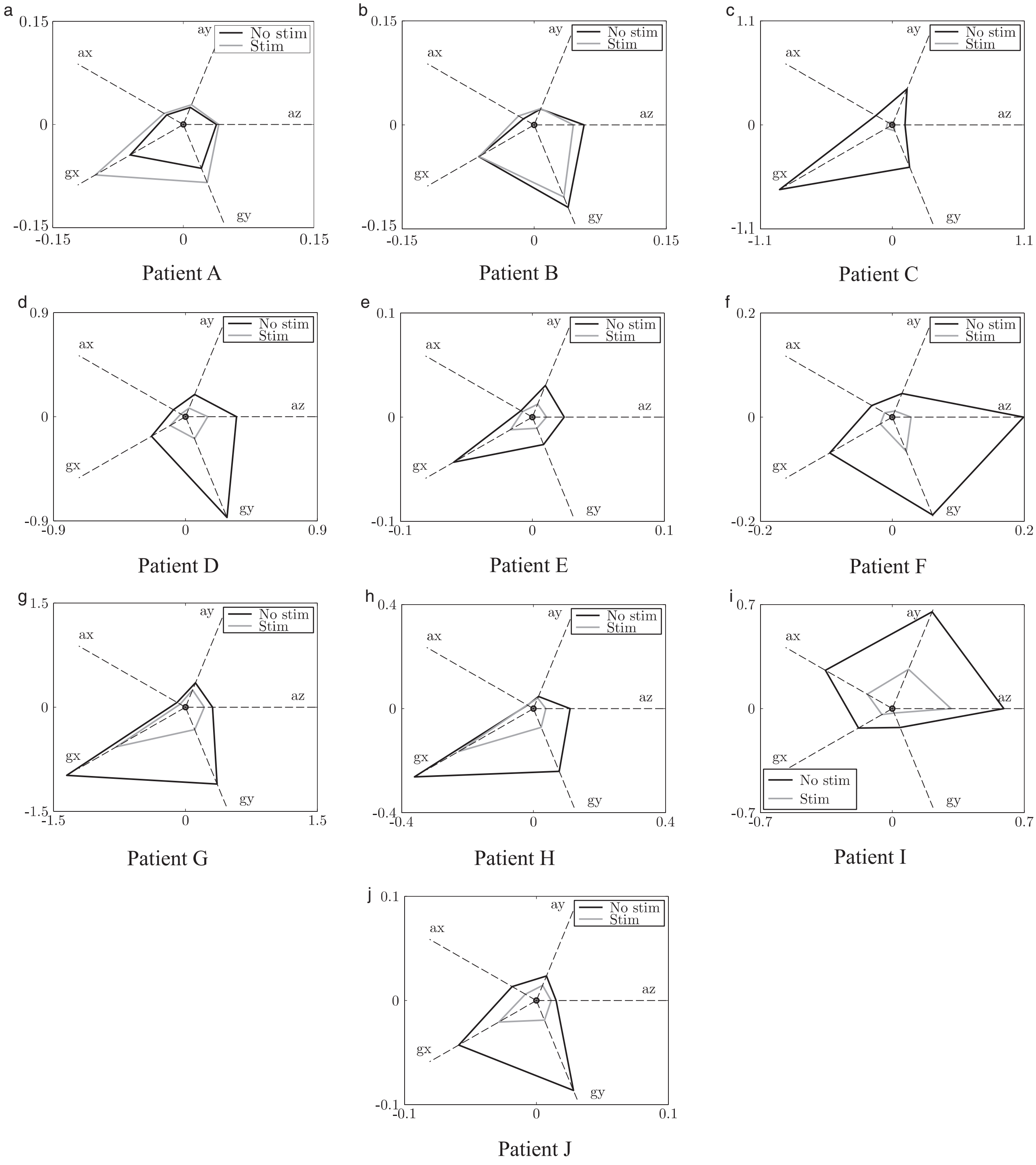

FIG. 1. Tremor amplitude (RMS value) for all participating subjects measured at each sensor; a refers to accelerometer and g to gyrometer. RMS values are shown in m/s^2 and rad/s, respectively. The axis limits are not the same for all patients, reflecting the different levels of tremor severity.

discussion. The figure illustrates one case where clear, immediate tremor attenuation was observed, as well as others where an adaptation phase was required or an extra instability emerged when the FES system was turned off. For each motion, the sensor presenting highest RMS value was chosen (accelerometer for Fig. 2a and gyrometer for Fig. 2b,c).

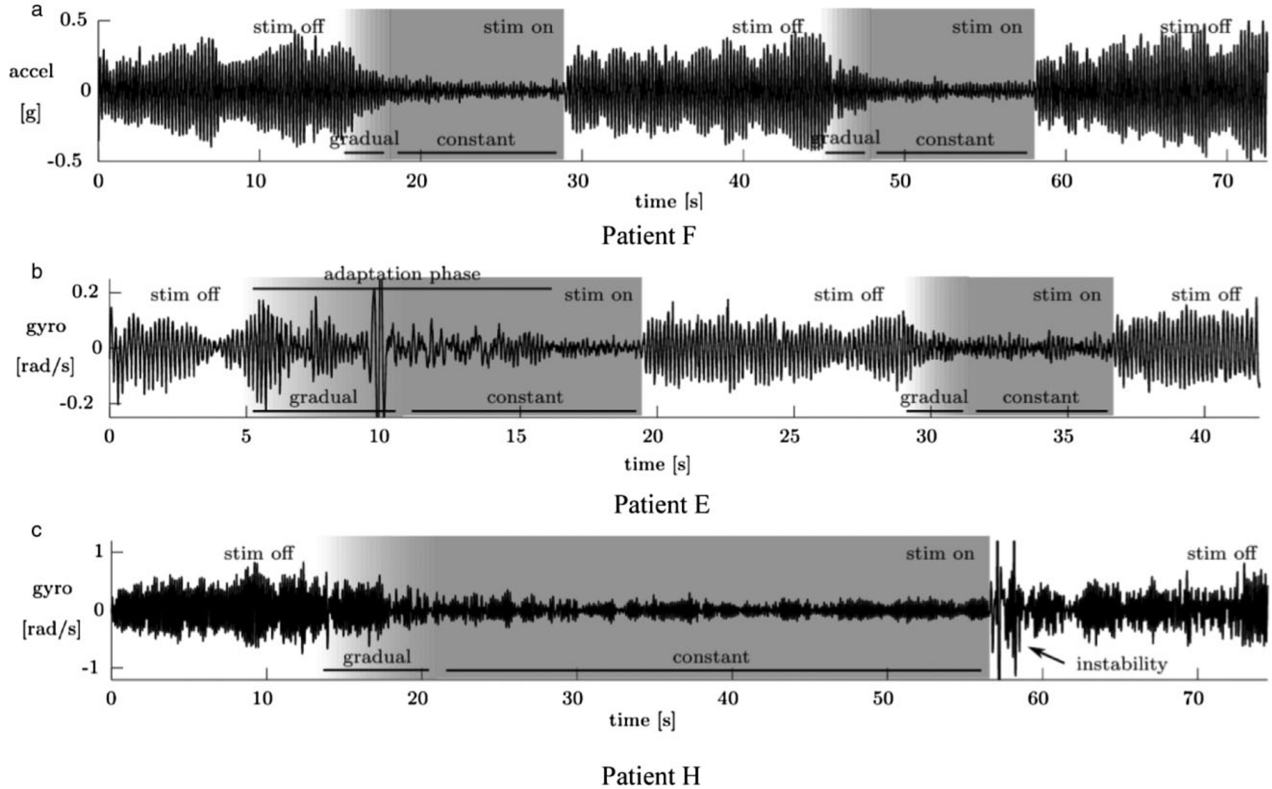

FIG. 2. Motion signals from illustrative trials. In (a), clear and immediate attenuation may be observed. The adaptation phase required in some patients to achieve better performance is depicted in (b). In (c), sudden instability occurring once the support from FES vanishes is illustrated. In all cases, the initial period when FES intensity is gradually increased is also depicted.

DISCUSSION AND CONCLUSIONS

Based on the illustrated results, it may be concluded that tremor attenuation based on fixed-intensity FES is feasible, as poor or limited effectiveness was observed in only two patients in a population of 10. In this section we present a qualitative discussion concerning the major related issues.

Clear immediate tremor attenuation was detected in patients presenting different tremor features (in terms of joint affected and tremor severity on the Fahn–Tolosa–Marin tremor rating scale) and in patients in whom different types of stimulation strategy were used (single muscle or pair of antagonist muscles). This may indicate that various phenomena are involved in the reduction of tremor amplitude, such as FES-induced co-contraction increasing joint impedance, reduction in tremor activity due to recruitment of muscle fibers presenting tremor activity, or tremor attenuation due to unknown effects related to the stimulation of afferent pathways. Even though all these distinct hypotheses are plausible, further conclusions cannot be developed based on the obtained data, given the limited knowledge on muscle dynamics in ET and the diversity of FES-induced muscle responses observed in different patients.

Concerning the circumstances where attenuation was preceded by an adaptation phase (e.g., Fig. 2b), we believe that the performance was greatly influenced by involuntary reactions to the FES-induced contraction. As none of the patients had any previous experience with FES, the effect is unsurprising. For this reason, we believe patients who present an adaptation phase before tremor attenuation may greatly benefit from adequate training. It may be observed from Fig. 2b, for instance, that there was no adaptation phase in the second stimulation period. Indeed, the adoption of stimulation trials featuring different intervals enabled observation of higher tremor attenuation for longer trials in some patients. Other observed negative effects may potentially be reduced with practice, such as sudden instability generated once the support from FES is removed (e.g., Fig. 2c).

There were also two cases where no positive effect was observed during the experimental sessions (tremor increase in one, no significant improvement in the other). Considering that only in two patients was it impossible to verify reduction in tremor amplitude using the tested strategy, we believe that the lack of success in these sessions was caused by the limitations of the experimental protocol. For the other patients, in whom the method produced a positive but considerably inconsistent response (according to subjective judgment by the patient), it may also be the case that these limitations affected the overall performance of the method.

Among the most significant weaknesses of the experimental protocol, one important difficulty was related to electrode placement in elderly patients, particularly for stimulation of multiple muscles (as stimulation diffusion increases considerably in such cases). Indeed, for most patients it is hard to imagine real-life applications without improved electrode technology, such as implantable or multipad electrodes (15).

Another significant issue is related to inherent tremor variability. As the study used a within-subject experiment design where FES was the manipulated variable, ideally all other aspects that affected the response should have been kept constant. Indeed, intrinsic fluctuations of ET amplitude may greatly affect the computed tremor reduction. Employing static tasks reduced the variability in tremor amplitude, but in some cases fluctuations remained intense due to subject-specific features, such as voluntary contractions. A longer protocol involving multiple sessions would have enabled the patients to get used to FES, which was not possible in our study, which was based on single sessions with each patient.

In view of these experimental limitations, our future work will focus on trials in patients based on multiple experimental sessions and will involve more careful choice of muscle(s) to stimulate, as well as proper evaluation of the functional benefit provided by the method. A longer protocol including an initial training period may reveal whether the negative effects observed in some patients can be suppressed. Finally, using recorded motion and patient evaluation of fatigue and sensitivity, the ultimate goal is to compare different compensation strategies in controlled scenarios.

Nevertheless, this study has demonstrated the feasibility of reducing tremor amplitude by applying fixed-level FES to the muscles acting on the joint concerned. Compared with alternative systems such as the antiphase approach, the method tested in this study may indeed present some advantages. Firstly, the applied stimulation may be more comfortable and predictable, possibly increasing acceptance among potential users. The resulting device may also be more compact and simpler, permitting the use of less sophisticated and cheaper hardware. Considering that tremor often propagates from proximal to distal joints, this may also be an important feature. Indeed, in antiphase FES tremor compensation, unstable performance in proximal joints may increase tremor of the hand, while in the method used in this study, the effect of stimulation is intrinsically stabilizing. Furthermore, the results also showed that tremor was not shifted to another plane of motion, which would indicate that the pathological motion was not actually compensated for and would consequently be a great disadvantage. Finally, an additional important result concerns the fact that tremor reduction was not always clear and immediate. Indeed, given the observed phenomena of adaptation periods previous to tremor attenuation and sudden instability after stimulation, we infer that tremor compensation strategies based on FES should include a mandatory training phase during which the patient will be able to learn the motor patterns to use during stimulation.

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