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Attenuation of Pathological Tremors by Functional Electrical Stimulation II: Clinical Evaluation

Manouchehr Javidan,* Josef Elek,† and Arthur Prochazka*

*Divisions of Neurology and Neuroscience
University of Alberta
Edmonton, Alberta, T6G 2S2 Canada

†Neurologische Klinik der Universität Bonn
Germany

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In this study we evaluated a technique for tremor suppression with functional electrical stimulation (FES), the technical details of which were described in the previous paper. Three groups of patients were investigated: those with essential tremor, parkinsonian tremor, and cerebellar tremor associated with multiple sclerosis. In each group, tremor was attenuated by significant amounts (essential tremor: 73%; parkinsonian tremor: 62%; cerebellar tremor: 38%). These attenuations were in good accord with predictions based on the dynamic analyses and filter designs derived in the previous paper. With filters "tuned" to the lower mean tremor frequency encountered in the cerebellar patients, more attenuation was possible in this group as well. We identified some practical limitations in the clinical application of the technique in its present form. The most important was that in daily use, only one antagonist pair of muscles can realistically be controlled. At first sight, this restricts the usefulness of the system to patients with single-joint tremors. However, the concomitant use of mechanical orthoses may broaden the scope of application.

Keywords— *Tremor suppression, Cerebellum.*

INTRODUCTION

In the previous paper (7) we described a new method for selectively attenuating tremor by using closed-loop functional electrical stimulation (FES) to activate the tremorogenic muscles out-of-phase. The potential advantage of such a system is that it does not rely on mechanical loading of the extremity (2), nor on externally powered electromechanical devices (6). In principle, the selective "tuning" of attenuation to tremor frequencies, leaving slow voluntary movements unimpeded, offers a superior selectivity to that achievable by simple inertial or viscous loading. However, *a priori*, there also seemed to be some potential disadvantages. In its present form the system

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Address correspondence to Dr. A. Prochazka, Division of Neuroscience, Room 507, Heritage Building, University of Alberta, Edmonton, Alberta, T6G 2S2 Canada.

can only stabilise tremor in one antagonist muscle pair. This seemed to rule out its efficacy in the multijoint and multidirectional tremors often seen in patients. Electrical stimulation can sometimes elicit reflexes, which might interfere with the performance of the system. Pathological tremors can be variable in amplitude and frequency, particularly in relation to behavioural task and context; in its present form, the system is tuned to suppress a preselected band of tremor frequencies, and becomes rapidly ineffective outside this band. Patients might find continuous phasic electrical stimulation uncomfortable. Finally, it was unclear whether the dynamic characteristics of response in the patients would be adequately represented by data from normal subjects.

In this paper we describe the results of trials evaluating tremor suppression with FES in three groups of patients: those with essential tremor, parkinsonian tremor, and cerebellar tremor. We found that tremor in all three disorders could indeed be substantially suppressed with this technique. The practical application of the method in a clinical or home setting is discussed, with reference to hybrid systems which include stabilising orthoses. A preliminary report of this work has been published recently (3).

PATIENTS AND METHODS

Clinical Assessment of Patients

A total of 24 patients were referred from the University of Alberta Hospital's inpatient neurology unit, outpatient neurology clinics, and multiple sclerosis research clinic. The patients were diagnosed as having three categories of tremor: essential tremor, parkinsonian tremor, and cerebellar tremor. All patients were examined clinically by one of the authors (M.J.) and videotaped prior to and during the trial. Three patients with essential tremor, four patients with Parkinson's disease, and six patients with cerebellar tremor, due to multiple sclerosis, were selected. The only criterion for selection was a disabling rhythmical tremor involving the wrist (mostly in essential and parkinsonian tremor) and/or the elbow (in cerebellar tremor). Patients with mild resting or postural tremor not interfering with daily work, and patients responsive to tremor-suppressing medications were excluded, as were two severely depressed patients. One patient with the diagnosis of Parkinson's disease also had postural tremor and had not responded to antiparkinsonian therapy. Another patient diagnosed as having essential tremor also had rest tremor and other minor parkinsonian features. Although medication was discontinued two to three days prior to the trial in most of these patients, three patients remained on medication throughout. Subjects or their guardians gave their written consent to the experiments, in accordance with the requirements of the University of Alberta Human Ethics Committee and the Declaration of Helsinki.

Functional Electrical Stimulation Trials

The experimental arrangement was similar to that described in the previous paper, except for some small simplifications designed to minimise inconvenience to the subjects. For wrist experiments, the subject's arm was completely free to move, hand displacement being monitored by a miniature displacement transducer consisting of a compliant elastic band attached to a small cantilever strain gauge. The ends of the gauge, which were stretched across the joint on the palmar side approximately in line with the middle finger, were attached to the skin with double-sided adhesive tape. It is worth noting that the frequency response of this type of gauge is flat to 50 Hz provided that the elastic band has not deteriorated. We found that phase advances, due to age-related viscosity in the elastic material, alter the open-loop transfer functions and can seriously affect the efficacy of closed-loop stimulation. This problem will be addressed again in the Discussion. For elbow movements, patients were seated comfortably in the experimental chair (illustrated in Fig. 2 of the previous paper), their forearm supported by the pivoting armrest. In this case, the transducer monitored the movements of the armrest rather than the subject's forearm, to avoid the problem of muscle mobility (7).

Pregelled adhesive electrodes (Chattanooga Corp.) or moistened pads were used as cathodes to activate the extensors and flexors selectively. The indifferent electrode (anode) consisted of a moistened sponge strip wrapped around the wrist, or around the ipsilateral leg just below the knee.

Initial Parametric Adjustments. All trials in the patients were with closed-loop systems, using filters described in Eqs. 5 and 7 of the previous paper (wrist and elbow, respectively). The underlying assumption was that the open-loop transfer functions obtained empirically in normal subjects were similar to those of the patients' load-moving muscles. Instead of the rigorous setting-up procedures described in the previous paper to ensure specific, balanced background forces, in the patient trials we simply increased the tonic level of stimulation to the flexors and extensors separately until contraction thresholds were just reached. Loop gain was then gradually increased with flexor stimulation alone until instability just occurred (the hand or forearm started oscillating, typically at 7–9 Hz, as expected from the f_{180} values derived in normal subjects (7)). The same was now done with extensor stimulation alone. Next, with *concomitant* flexor and extensor stimulation (effectively doubling net loop gain) overall gain was reduced until marginal stability was reattained (brisk taps applied to the hand eliciting a damped oscillation). From this reference point, gain was now further reduced by specific amounts (e.g., 6 dB, equivalent to 50%).

Movement Trials. In patients with resting tremor, the efficacy of tremor suppression was evaluated in the absence of voluntary movement of the affected limb. In several cases, tremor was potentiated prior to switching on the stimulator by distracting the patient with a simple task with the contralateral hand such as knee-patting. Patients were then asked to track slow movements of the experimenters' hand, or of a moving-bar target on a video screen, the surface of which was just beyond the subject's fingertips. In patients with postural and intention tremor, functional tasks such as attempting to bring a half-filled cup to the mouth were also tested. The attenuation of the amplitude of both tremor and voluntary displacement in these various classes of movement during short periods of closed-loop stimulation of unexpected onset and duration was analysed off-line.

Analysis. The subjects' wrist or elbow movements and concomitant stimulator command signals were recorded on cassette tape (TEAC R61 instrumentation recorder) and some trials were videotaped. Selected segments of the analogue data were digitised off-line using a Cambridge Electronic Design (CED) 1401 laboratory interface linked to an Olivetti M28 microcomputer. The data were digitised, displayed, and printed (Hewlett Packard Laserprinter) with the use of CED "Massavg" software (7). Power spectral analysis was performed with CED "Waterfal" software (7), with sampling rates of 50/s.

RESULTS

Patients tolerated the electrical stimulation very well. After a minute or two of "getting used" to it, 11 of the 12 patients reported little or no discomfort, and felt that long-term use would be acceptable. One patient reported muscle fatigue after a 20-minute stimulation session, and did not feel that this would be acceptable if the system were used daily. Mild muscle fatigue was experienced by three or four patients after sessions in which tremor, and electrical stimulation to suppress it, had occurred continuously.

Figure 1 serves to illustrate typical results. The patient was a 54-year-old male with familial (essential) wrist tremor of unknown etiology. The filter used in this patient is that described by Eq. 5 and Fig. 6b of the previous paper. At a loop gain of about

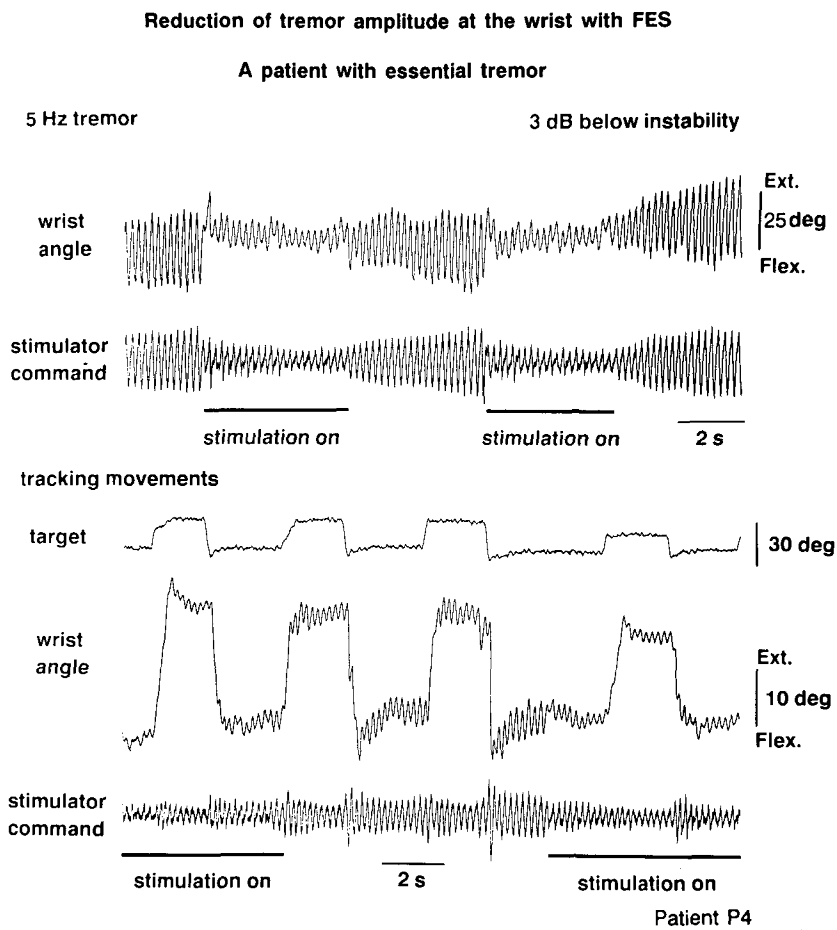

FIGURE 1. Electrical suppression of tremor in a patient with essential tremor. Top panel shows wrist angle and the stimulator command signal derived from it. Horizontal bars indicate when closed-loop electrical stimulation was present. An immediate and enduring reduction in tremor amplitude is apparent. The lower panel shows that the electrical stimulation did not significantly interfere with voluntary tracking of a slowly moving target (middle trace), yet the superimposed tremor was attenuated.

6 dB (3 dB below that at which stability was marginal, established as described above in the Methods), tremor was reduced by about 3:1 as anticipated (attenuation = (1 + gain): ref. (7)). The patient was able to perform accurate tracking movements during closed-loop stimulation (Fig. 1 bottom panel), and indeed because the superimposed tremor was attenuated, the overall accuracy of tracking was enhanced.

A more detailed evaluation of these data was obtained by computing the power spectra of segments of the displacement signal before, during, and after stimulation. This form of analysis, done with the "Waterfal" software (7), is shown in Fig. 2. Panel b shows consecutive spectra computed from 20 overlapping 4-s "slices" of the recording in panel a (same patient as in Fig. 1, but a different trial). Panel c shows averages of slices 6–10 ("FES off": solid line) and slices 15–19 ("FES on": dashed line). Several interesting points emerge. First, it is quite clear from Fig. 1c that tremor was suppressed during stimulation, the mean power attenuation at the fundamental frequency (3.4 Hz) being 16:1 (equivalent to an amplitude attenuation of 4:1; i.e., 12 dB or 75%). Second, tremor suppression was instantaneous and enduring. Third, the fundamental frequency of tremor was unchanged during stimulation despite the likely disruption of proprioceptive input resulting both from the diminished movement and the direct electrical stimulation of muscle afferents.

A similar set of data from a parkinsonian patient is presented in Fig. 3. This patient was a 53-year-old woman with a long-standing prominent rest tremor associated with other features of Parkinson's disease. Tremor was mainly observed in the right hand and wrist with significant involvement of the fingers. Her tremor had not responded well to antiparkinsonian medications. Tremor was suppressed during closed-loop stimulation, the mean power at 3.4 Hz showing 28:1 attenuation (Fig. 3c) equivalent to an amplitude attenuation of 5.3:1 (i.e., 14.5 dB or 81%). Again, the frequency of the residual tremor was similar to that of the unattenuated tremor. In this patient there was an underlying irregular dysmetria, which seemed to be "unmasked" when the tremor was suppressed. This may have been due, in part, to an interaction with the continuing finger tremor, not suppressed by stimulation. We observed this unmasking effect in all four parkinsonian patients.

Finally, the results from a cerebellar patient with tremor about the elbow are presented in Fig. 4. This was a 32-year-old man with long-standing multiple sclerosis. He had clinical evidence of marked abnormalities of the spinal cord and brain stem. Severe intention tremor and ataxia indicated cerebellar involvement. The patient was wheel-chair bound and his arm tremor was such that he was unable to feed himself or hold a cup steadily enough to be functional. None of the standard medications had suppressed the tremor. Heavy inertial loading attenuated the tremor but severely impaired movement and endurance.

The patient tracked a moving bar displayed on a video screen, the target displacement shown in the lower trace of Fig. 4A. Stimulation of elbow flexors and extensors was turned on unexpectedly during this tracking period. Figure 4c shows that the power content of the tremor was attenuated by 6.2:1, equivalent to an amplitude attenuation of 2.5:1 (8 dB or 60%). The amplitude of the underlying voluntary tracking movements was not noticeably changed as judged from the displacement record of Fig. 4a. Table 1 indicates that the level of suppression of tremor in this patient was at the upper end of the range in the cerebellar group (mean 38% reduction compared to 61% in parkinsonian tremor and 73% in essential tremor). Unfortunately, we only noticed after having tested five cerebellar patients that their mean tremor frequency

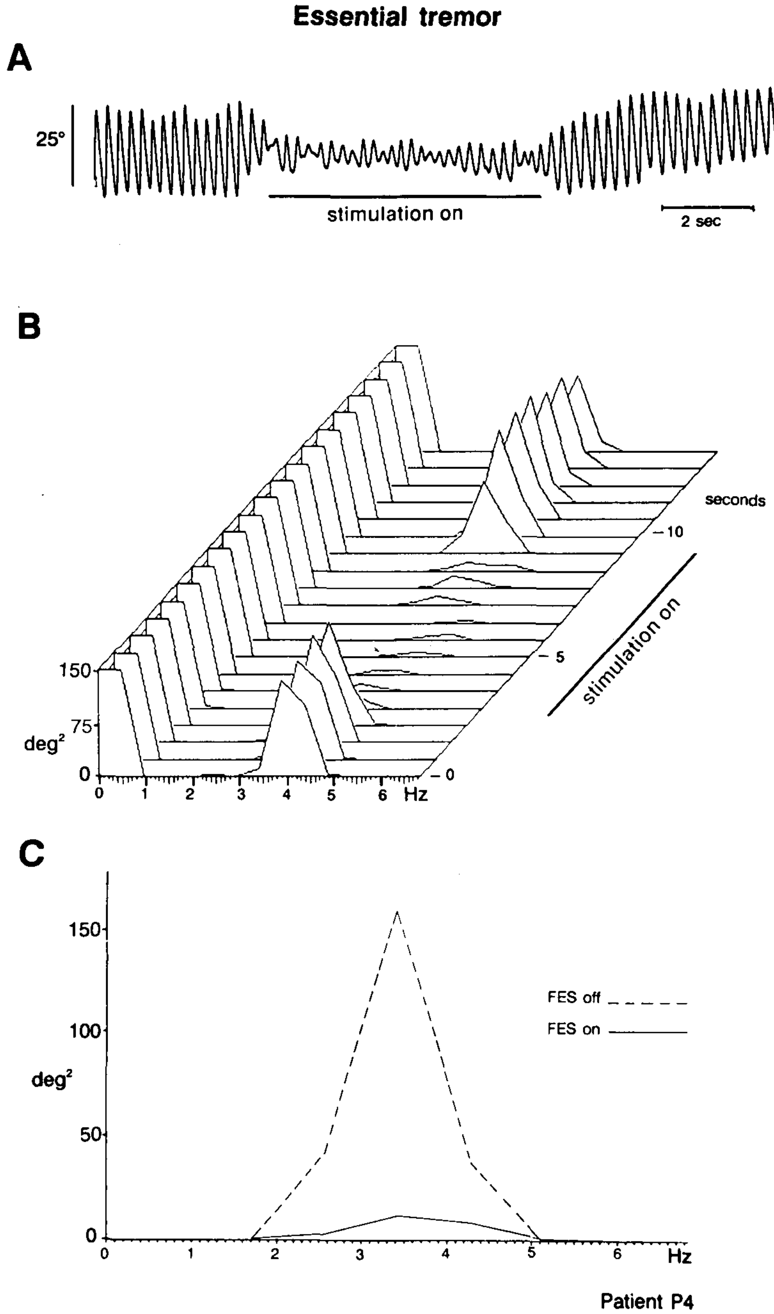

FIGURE 2. Power spectral analysis of further data from the same patient. (a) The 16-s segment of displacement signal was divided into 20 staggered and overlapping "slices" each of 4-s durations. (b) The power spectrum of each slice was computed and plotted in a three-dimensional display. Stimulation applies to the middle nine segments of this display, the 3–4 Hz tremor peaks being clearly attenuated. (c) The means of the power spectra *with* stimulation (slices 6–10) and *without* stimulation (slices 15–19) are shown, revealing a 16:1 attenuation of the 3.4-Hz peak during stimulation.

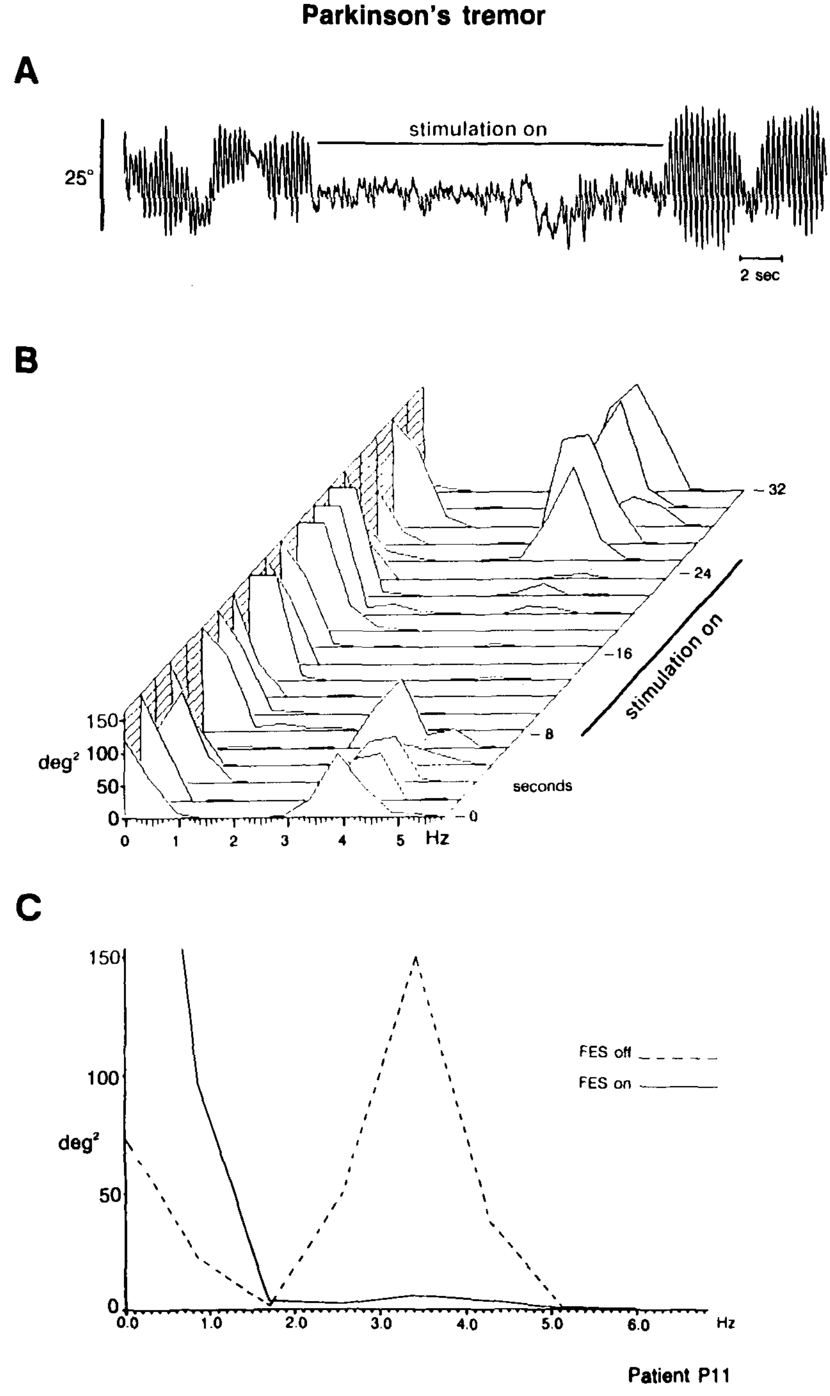

FIGURE 3. Similar data for a patient with Parkinson's disease. Attenuation of the tremor was associated with the unmasking and slight augmentation of slower irregular movements. Tremor power at 3.4 Hz was attenuated by 28:1 and frequency was unaffected.

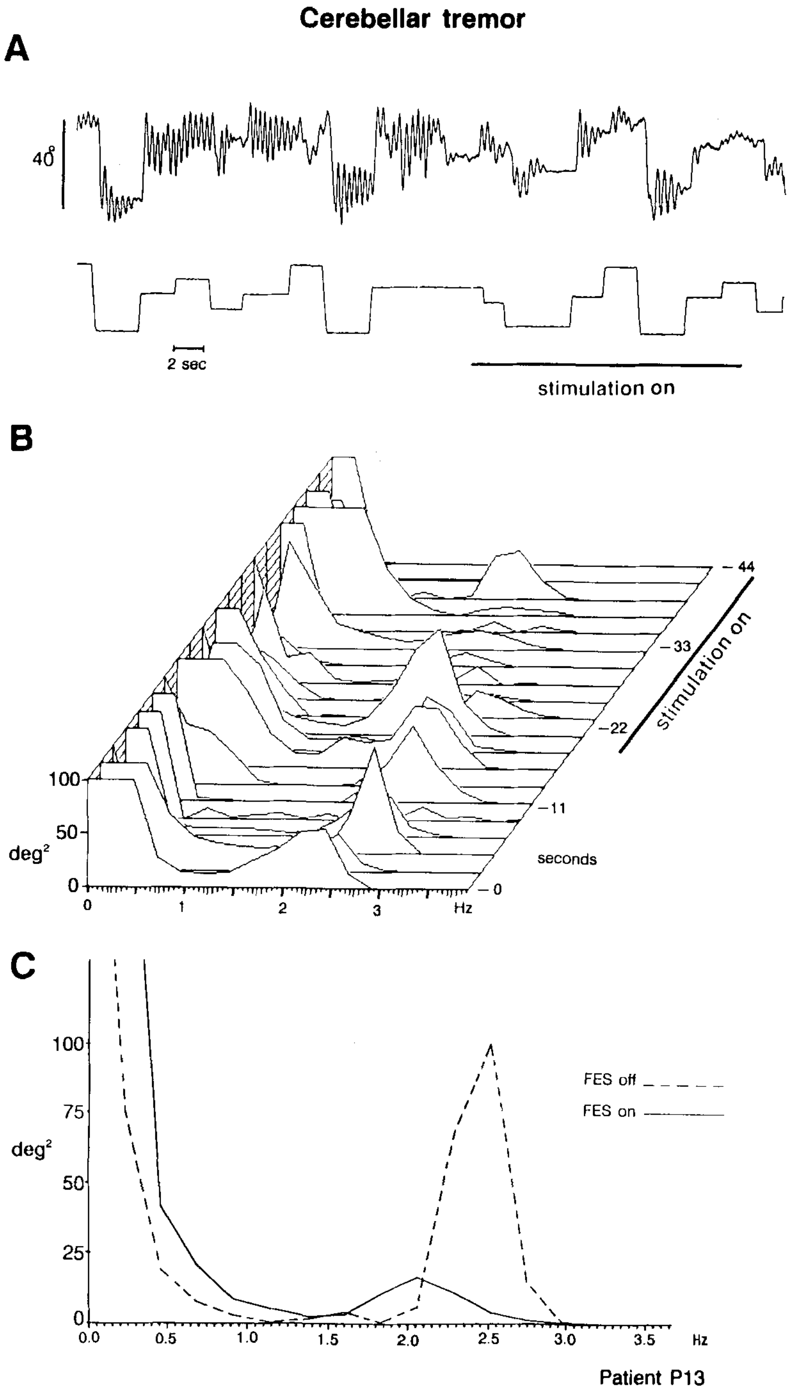

FIGURE 4. Similar data for a patient with cerebellar tremor associated with multiple sclerosis. In this case, the patient was tracking a moving-bar target on a video screen. The tremor peak at 2.5 Hz was attenuated by 6.2:1 and shifted to 2.1 Hz during stimulation.

TABLE 1. Tremor attenuation in patients using FES system.

Patient & Tremor	Frequency Stimulation Off	± SD (Hz) Stimulation On	*n*	*t*	Significance ($p < 0.1$)	Mean % Attenuation
2 Essential	4.5 ± .2	4.6 ± .1	13	1.00	no	72
3 Essential	2.7 ± .1	2.7 ± .2	9	1.14	no	55
4 Essential	3.9 ± .05	3.5 ± .2	4	2.38	yes	91
6 Parkinson	4.9 ± 0.5	5.0 ± .3	11	1.26	no	54
7 Parkinson	5.4 ± .3	5.4 ± .3	11	0.45	no	57
10 Parkinson	4.4 ± .1	4.3 ± .2	6	1.57	no	69
11 Parkinson	4.5 ± .2	4.6 ± .1	13	0.86	no	66
5* M.S.	2.8 ± .2	2.6 ± .3	5	1.24	no	66
8* M.S.	2.5 -	2.5 -	2	-	-	0
12* M.S.	3.0 ± .2	3.1 ± .4	4	0.32	no	10
13* M.S.	2.0 ± .4	1.6 ± .1	3	1.57	no	50
15* M.S.	1.9 ± .1	2.0 ± .2	9	1.57	no	36
15† M.S.	2.0 -	1.6 -	2	-	-	68

n: number of paired spectra (stimulation on vs. off); *t*: calculated Student's t value for comparison of means; *3-Hz filter was used; †2-Hz filter was used.

was significantly lower than in the other groups (2.4 Hz cf. 3.7 Hz in essential tremor and 4.6 Hz in parkinsonian tremor). The elbow filter used in these trials was that of Eq. 7 and Fig. 7b of the previous paper, designed to be maximally effective in the 3–4 Hz range. In patient 15, 68% attenuation was obtained with the use of the 2-Hz filter of Eq. 8 and Fig. 7a of the previous paper. An interesting feature of the responses in Fig. 4 was the shift in frequency from 2.4 Hz to 2.1 Hz during stimulation.

DISCUSSION

Much was learned from this pilot study on the possible use of FES in controlling tremors. First and foremost, it was clear that significant attenuation was possible in the three main types of pathological tremor. Most of the reservations alluded to in the Introduction may be rejected. Patients generally tolerated the electrical stimulation well. The natural waxing and waning of tremor amplitude did not disrupt the performance of the system, nor were the variations in tremor frequency within an individual patient sufficient to degrade tremor suppression. Other than brief startle responses when stimulation was turned on abruptly, the motor consequences of stimulation were consistent with direct muscle activation only, and there were no major components of response indicative of reflexive action. This is not to say that reflexes were absent or unaffected by the intervention (see below), but merely that they did not significantly change the behaviour of the closed loop from that expected from direct stimulation alone.

We could not measure the open-loop characteristics of response to electrical stimulation in patients because of their ongoing tremor. The filters used were, therefore, based on data from normal subjects on the assumption that patients' muscles would respond similarly. We feel that this assumption was valid, for the following reasons:

In the patients the threshold of instability was used as the reference point for the setting of loop gain. From the corresponding reference point in normals (e.g., at 8 Hz, Fig. 6b of previous paper), we could determine the expected loop gain at the tremor frequency for a setting corresponding to say 3 dB below instability. From this followed a prediction of tremor attenuation at this setting if the above assumption were valid. Predictions were accurate to within 3 dB and so we conclude that the response dynamics of normals were indeed similar to those of the patients we studied. This is not too surprising, since the patients' muscles were generally in good condition, and well exercised by the persistent tremor.

In two of the three patients with essential tremor, and in all of the parkinsonian tremors, frequency was remarkably constant in the face of the major changes in proprioceptive input likely to result from the movement attenuation and the electrical stimulation of afferents. In the parkinsonian patients, additional irregular involuntary movements were "unmasked" by stimulation. This we attribute to an interaction with continuing finger tremor, and may be related to the waxing and waning of tremor amplitude seen in Parkinson's disease. The constancy of the fundamental frequency component during stimulation supports the notion that parkinsonian and essential tremors are largely central in origin, and relatively uninfluenced by peripheral input (1 & 5, but see also 4 & 9).

In some trials, tremor frequency in cerebellar patients 5, 13, and 15 changed during stimulation (e.g., Fig. 4), but statistically this was not significant at the $p < 0.1$ level (however, note that in patients 13 and 15 in all only 5 paired comparisons of spectra were available). If our impression is correct, that frequency is indeed altered by stimulation in these patients, this would be consistent with a peripheral contribution to this type of tremor. Admittedly, there is also the further possibility of a generalised arousal response to electrical stimulation in these patients, which might tonically influence an otherwise centrally generated rhythm.

Practical Application

While this study showed that in principle FES could provide long-term tremor suppression in patients for whom tremor is not sufficiently reduced by medication, some basic limitations became apparent and a number of practical problems were identified. The main limitation in a system intended for daily use is that with the currently available sensors and electrodes, it is unrealistic to aim to control more than one pair of antagonist muscles at a time. At first sight this would seem to restrict application to the relatively small number of patients with tremor confined largely to one joint. However, the use of splints and other mechanical supports, in conjunction with the present FES system, may greatly broaden its scope. For example, in severely incapacitated individuals with multiple sclerosis, we are presently testing an arrangement similar to that shown in Fig. 2 of the previous paper, whereby the forearm is supported on a horizontally pivoting armrest shaped to enclose the wrist so that pronation-supination tremor is mechanically limited. These simple constraints effectively reduce the task of FES tremor suppression to a single degree of freedom, namely elbow flexion-extension. With this hybrid system, patients with severe tremor who otherwise could not feed themselves, can bring food to their mouths in a controlled way. The armrest assembly is clamped to a high table allowing wheelchair access. Food placed on the table surface is at chin height, and the armrest swings through a 90° arc about

5 cm above this, allowing the patient to pick up food and move it to his or her mouth. Convenience in use is a major factor in the success of active orthotic devices. For daily use we envisage patients using pregelled self-adhesive electrodes, which may be worn for up to a week. The patient's wheelchair is pushed up to the table, his or her forearm is placed on the armrest, three snap-lock connections are made to the electrodes, and the system is turned on. The further practical problems we encountered were as follows:

1. *Electrode placement* could vary somewhat between individuals though not generally from one trial to the next in a given person. In chronic use surface electrodes have a number of drawbacks, and so in patients who benefit in a major way from FES tremor suppression, percutaneously implanted wire electrodes (8,10) might provide a more convenient alternative.
2. *Initial gain and offset adjustments* must be set accurately for good tremor attenuation. Though the design of self-calibrating devices is feasible, this would only be worthwhile if the basic technique comes into widespread use. For the present, patients or support personnel would have to learn this procedure. Provided that electrode placement and impedances do not vary, the settings for an individual should remain constant for an indefinite period of time. However, in practice it will probably be necessary to check them at regular intervals.
3. Mild *fatigue* occurred after prolonged stimulation in some cases. One patient judged the discomfort due to fatigue to be unacceptable in relation to a possible long-term application, though intermittent stimulation might avoid this problem, and muscles would develop fatigue-resistance within weeks.
4. *The displacement sensors* used in this study could in principle allow free movement of the arm. However, in practice we found that they only operated satisfactorily for flexion-extension tremor at the wrist. Although elbow flexion-extension tremor could sometimes be suppressed with the use of one of these transducers, this was generally unsatisfactory for two main reasons: First, tremor about the elbow is often complex, shifting between flexion-extension, pronation-supination, and abduction-adduction; control of flexion-extension tremor alone does not bring much functional benefit. Second, muscle bulging distorts the signal monitored by a surface-mounted transducer (7). The problem is minor at the wrist but significant at the elbow. Transducers of another design may circumvent this problem.

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