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Frequency Analysis of Involuntary Movements during Wrist Tracking: A Way to Identify MS Patients with Tremor Who Benefit from Thalamotomy

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Key Words

Frequency spectrum · Tracking · Tremor · Multiple sclerosis · Thalamotomy

Abstract

To identify those multiple sclerosis (MS) patients with disabling tremor who will benefit most from thalamotomy, measurements of frequency spectra of involuntary movements during visually guided wrist tracking were carried out in 11 consecutive patients with MS before and after ventrolateral thalamotomy. Thalamotomy was significantly more effective if patients had disruptive action tremor which appeared as a single peak in the frequency spectra. Such patients showed an average reduction of nearly 80% in tremor magnitude after thalamotomy. In comparison, surgery produced an average reduction of only 30% in 3 other patients who had action tremor but showed multiple peaks in the frequency spectra. Frequency analysis of involuntary movements identifies those MS patients with disabling tremor who benefited most from thalamotomy.

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Introduction

Tremulous movements of the arm caused by multiple sclerosis (MS) can be severely disabling and are often accompanied by other elements of ataxia, which literally means disorder or confusion [1–3]. Despite the variability in MS due to the size, number, location and pathogenic heterogeneity of lesions, thalamotomy [2, 4] or thalamic stimulation [5, 6] can reduce or totally eliminate MS action tremor. The functional outcome from stereotactic surgery however varies greatly [7]. Part of the problem is the difficulty in differentiating tremor from other ataxic components such as dysmetria by simple clinical examinations (for a recent review, see [8]). We felt that visually guided tracking tasks might be useful in predicting outcome of a ventrolateral thalamotomy in MS tremor. We have assessed tremor in MS using a visually guided ramp tracking task previously described [9] that enables us to measure involuntary movements of the wrist during tracking. Quantitative indices of tremor such as magnitude and frequency were obtained. Frequency analysis was particularly helpful for differentiating patients with predominant action tremor from those with other components of ataxia, because pathological action tremor manifests as a single frequency component in the spectrum. Other components of ataxia show a wide range of frequencies with multiple peaks. We present the results obtained from 11 consecutive MS patients who underwent thalamotomy to show how pre-operative frequency analysis can help to identify patients whose tremor is likely to respond best to thalamotomy.

Methods

Patient Details

With local ethical committee approval, we studied 11 consecutive MS patients (mean age 40 years, range 27–62; 8 females and 3 males) with disabling arm tremor undergoing thalamotomies at the Department of Neurosurgery, Radcliffe Infirmary, Oxford. All of the patients had been diagnosed as having laboratory-supported secondary progressive definite MS according to the MS classification of Poser et al. [10]. None of the patients complained of severe disturbance of position sense in the tested limb. Before testing, eyesight was assessed by displaying both visual cues at a distance of 1 metre, and all the patients reported that the display was easily seen. Additionally, no patient had either nystagmus or diplopia that could interfere with the perception of the visual cues. No attempt was made to correlate the movement disorder to lesions on brain scans, as there is no convincing published data suggesting this to be of use.

Visually Guided Wrist Ramp Tracking Task

Our wrist tracking task was previously described [8]. A 12 × 12 pixel square target was initially displayed in a stationary mode on a computer screen. In each trial, the target moved horizontally at a constant speed to the other side of the screen and then stopped. An adjustable plastic splint was used to support the patient's forearm and allowed for comfortable wrist flexion and extension over a range of 60° (± 30° around the neutral position) in a horizontal plane. Using this wrist flexion-extension movement, the patient moved a low resistance handle which was represented on the screen as a 6 × 6 pixel square. During the trials, the patient attempted to keep the cursor inside or as near to the moving target as possible, and then moved it back to the starting position in an unpaced movement of the wrist. Patients performed 16 trials, for each at four target velocities (13.64, 9.23, 7.5 and 5.5 deg/s) the order of which was randomly allocated. The voltage signals generated by the joystick during each task were amplified and digitally sampled (12-bit resolution at 70 Hz).

The wrist position signals were digitally differentiated and filtered using a zero phase, four pole Butterworth filter (corner frequency 25 Hz). A computer algorithm then selected tracking segments beginning 1 s after the target started moving until the end of the trial, thus eliminating the patients' initial reaction delay and acceleration phases. The mean movement velocity and the standard deviation of movement velocity were calculated for each trial and averaged over the 16 trials for each tested arm. For perfect, smooth tracking, the standard deviation of the movement velocity would be zero, while involuntary movements increase the standard deviation of the movement velocity. To index the change in involuntary movements after thalamotomy, we calculated the post/pre-operative percentage change in standard deviation of the movement velocity. The frequency composition of the records composed of all 16 tracking trials was computed using the Fourier transform.

Visually guided wrist pursuit tracking was assessed in these 11 patients 2 days before and 3 months on average after surgery.

Stereotaxic Thalamotomy

Pre-operatively, a T_1-weighted magnetic resonance image (MRI) scan using a 3D Turbo-FLASH sequence (TE 7 ms, TR 15 ms) and a Siemens 1.5-tesla Magnetom Vision Scanner is acquired. The surgery is covered with a 3 day course of intravenous methylprednisolone (1 g/day), commencing 1 day before surgery. Under general anaesthesia, the Cosman-Roberts-Wells (CRW™) head ring is fixed to the patient's head, low enough to acquire a CT scan of the entire skull. We prefer to use a general anaesthetic for this stage to avoid patient movement and for patient comfort. A stereotactic CT scan of the entire skull is acquired using 3-mm contiguous slices. Next, the MRI and stereotactic CT data are transferred to the StereoPlan™ (Radionics Inc.) workstation [11]. Using the ImageFusion™ (Radionics Inc.) software, the MRI is aligned to the stereotactic CT with at least three anatomic landmarks. Once alignment is complete, the ImageFusion software volumetrically correlates the MRI image set to the stereotactic CT, independently scaling X, Y, Z and all rotational axes. Using the StereoPlan software, the MRI, spatially corrected and volumetrically correlated to the stereotactic CT space is used for anatomic localisation of the thalamic target. Further anatomic verification is performed with the AtlasPlan™ module of StereoPlan. This coregisters the Schaltenbrand and Wahren Atlas to the patient's scans using the anterior and posterior commisures (AC and PC) as well as a lateral landmark (we compare the putamino-pallidal boundary of the patient's scan to that in the atlas). The AtlasPlan module displays the target on the Schaltenbrand and Wahren Atlas images.

Targets within the thalamus are chosen relative to the AC-PC line, in that for action tremor the target lies 10–14 mm lateral to the mid-commissural point (VOP). The choice of

VOP was based on our intra-operative observations in these patients that macro-stimulation and suppression of the action tremor was most effective when the electrode was positioned lateral to the mid-commissural point (i.e VOP) and less so when placed 3–5% mm posteriorly (i.e. VIM).

The trajectory can also be evaluated with the StereoPlan software setting the arc and collar angles. We use an entry point 1.0 cm anterior to the coronal suture and 2.0 cm lateral to the mid-line. Whilst planning the procedure, the patient has an arterial line inserted to monitor blood pressure, and the anaesthesia is reversed. The patient's systolic blood pressure is maintained 20 mm Hg below the pre-operative level, as we feel this reduces the risks of an intra-cerebral haemorrhage. We do not routinely shave the patient's hair but clean it on table with aqueous and alcoholic chlorhexidine and then shave a few hairs at the point of entry. A dermal skin punch is then used to incise the skin, the a 4-mm twist drill hole is made along the planned trajectory. The dura is then punctured with a biopsy cannula. This minimises any CSF leakage that could cause brain sag. The electrode (5 mm exposed tip and 1.8 mm in diameter) is than passed to the target, and macro-stimulation is performed. Tremor suppression should be achieved at 100 Hz and 0.75–1.5 V (pulse width of 1 ms). Capsular responses should not be elicited below 2 V. Lesions are placed 2.0 mm below, at the target and 2.0 mm above it. This achieves a volume of coagulation sufficient to ensure long-term tremor suppression in the majority of patients.

Results

Postoperatively, the standard deviation of the movement velocity was reduced by 65% in the whole group ($p = 0.01$; $n = 11$; paired t test) reflecting a significant decrease in the magnitude of the involuntary movements. Some patients, however, did much better than others (fig. 1), and they clustered into two groups. Eight patients (group 1) did well, with a residual tremor of 21 ± 17% of pre-operative levels, this was significantly better ($p < 0.05$, unpaired t test) than 3 patients (group 2) whose tremor was only modestly reduced to 70 ± 26% of pre-operative levels.

The pre-operative frequency spectra of the group 1 patients invariably showed a single sharp peak at 2.3–4.8 Hz (fig. 2), whilst the patients who did badly had frequency spectra with multiple peaks (fig. 3). In the poor outcome group, there were large peaks around 1 Hz reflecting voluntary tracking movements and error corrections. Additionally the tracking record showed that their tracking movements drifted behind the target projectile and broke into small steps (fig. 4). This decomposition of smooth movement indicates dysmetria which is not easily identified by clinical observation. Comparing pre- and postoperative spectra reveals that surgery suppressed the tremor component, but did not affect the other components in the poor outcome (group 2) patients, accounting for the poor overall reduction in their involuntary movements.

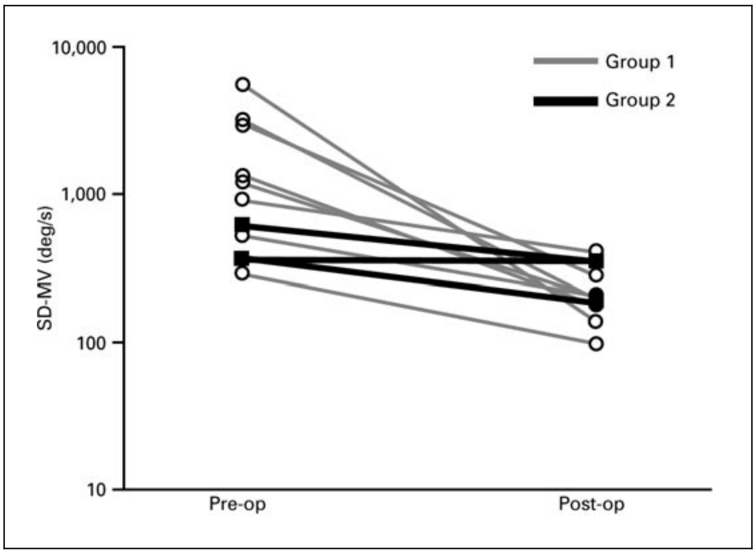

Fig. 1. Comparison of overall magnitude of involuntary movement pre- (Pre-op) and post-thalamotomy (Post-op) in a total of 11 cases. Group 1 (grey lines): 54–97% reduction in magnitude, n = 8; group 2 (black lines): 2–48% reduction, n = 3.

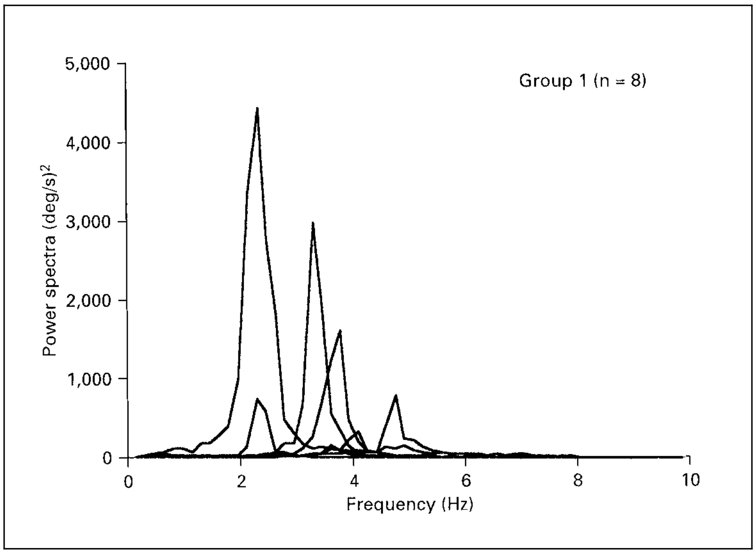

Fig. 2. Group 1. Pre-operative power spectra of 8 patients. Action tremor in each case had a single peak ranging from 2.3–4.8 Hz.

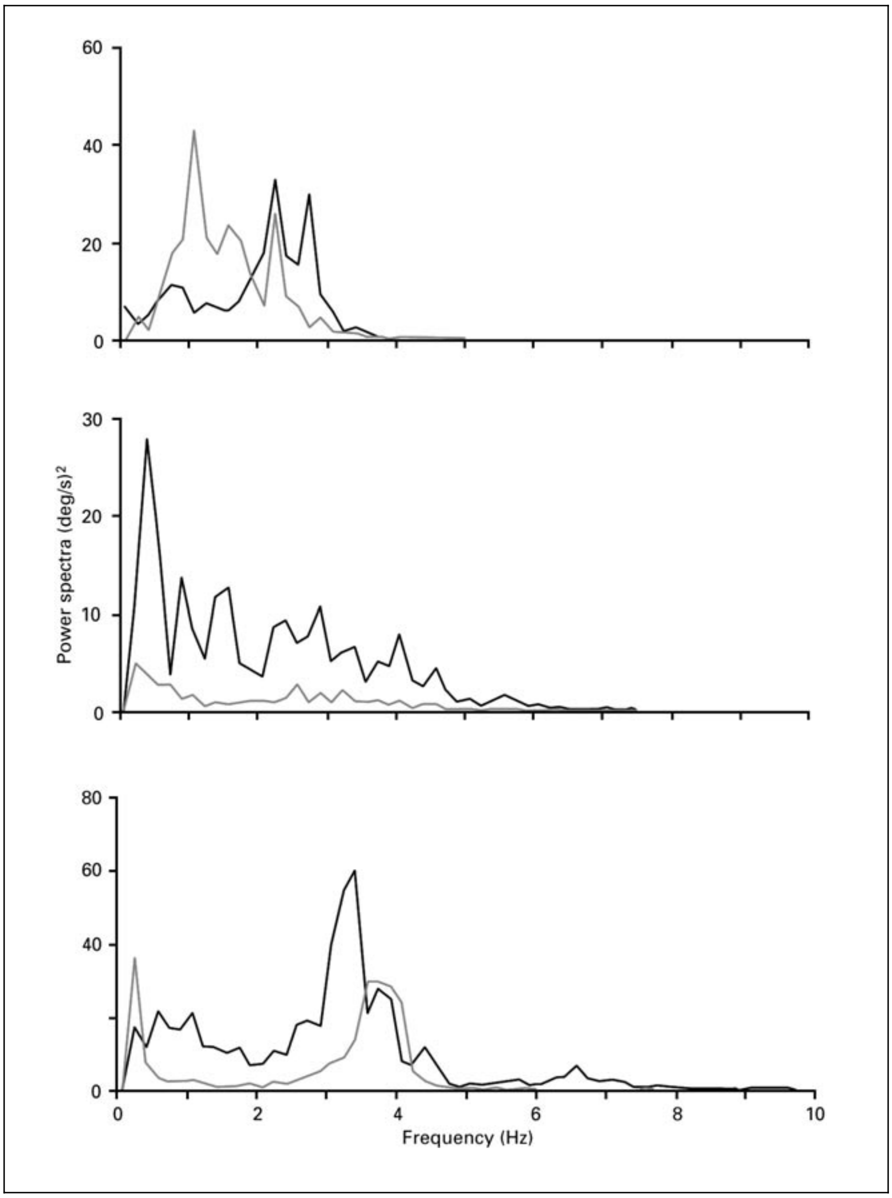

Fig. 3. Group 2. Pre- (black lines) and post-operative (grey lines) power spectra of 3 patients. J.Y. (top): pre-operative spectrum showed three peaks at 0.9, 2.4 and 2.9 Hz; post-operative spectrum showed significant reduction at 2.9 Hz, but new peaks appeared at 1.2 and 1.8 Hz. B.H. (middle): multiple peaks of relatively low amplitude ranging from 0.5 to 4 Hz reduced by thalamotomy. J.S. (bottom): peak at 3.3 Hz significantly reduced, that at 3.9 Hz did not change significantly.

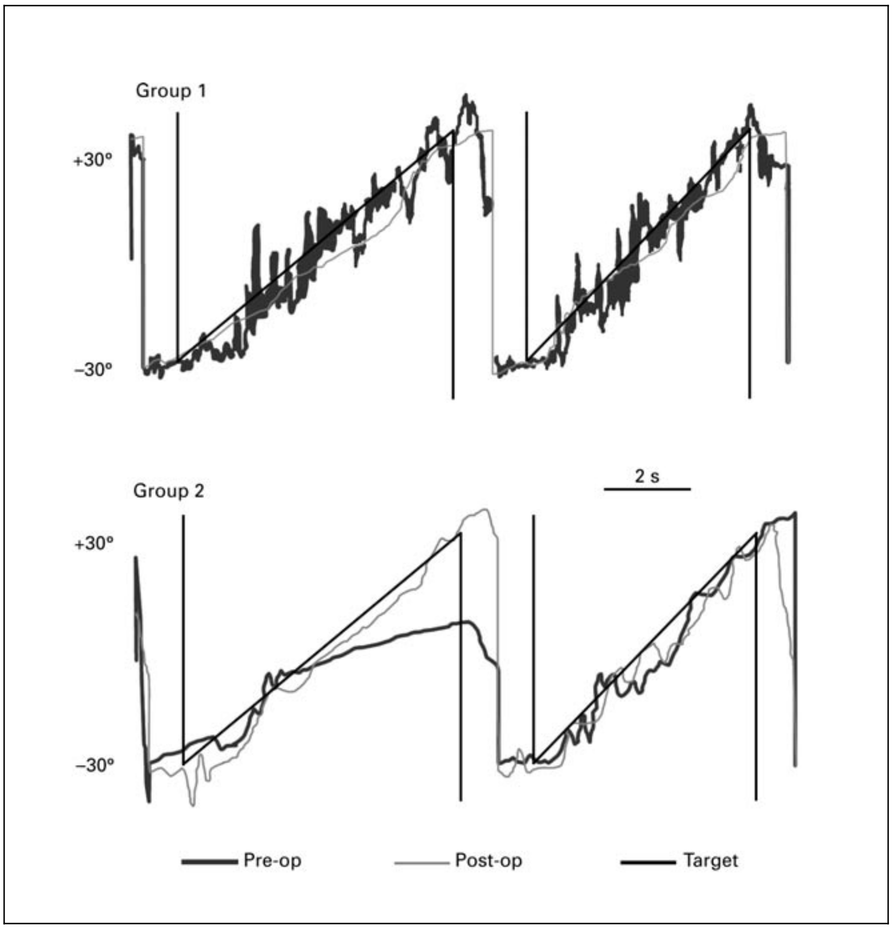

Fig. 4. Target (black), pre- (dark grey) and postoperative (light grey) tracking. Group 1 patients showed significant reduction of action tremor (upper traces) and tracking became smoother and more accurate. Group 2 (J.Y., lower traces) tracking movements were slower than target and decomposed. Postoperative low-frequency involuntary movements remained without significant reduction in overall magnitude.

Table 1 shows the long-term results in all patients. Of the 8 patients in group 1, 1 patient died at 2 years follow-up because of progression of MS and 1 died at 4 years follow-up of metastatic breast cancer. All patients in this group derived benefit from surgery, varying from restoration of the ability to write legibly or feed themselves to just being easier to nurse. No such functional benefits followed surgery in patients from group 2.

Table 1. Patient details and long-term results

Pt.	Sex	Age years	Duration of MS, years	Dur. tremor, years (type)	Operation	Compli-cations	Results[1]	Benefit at last F/U[1]	F/UP period years
1	M	27	9	10 (2)	R VOP	–	poor	–	5
2	M	46	7	7 (2)	L VOP	–	poor	–	6
3	F	52	20	5 (2)	L VOP	–	poor	–	5
4	F	35	11	10 (1)	R VOP	–	moderate	+	4
5	F	43	15	1 (1)	L VOP	transient dysarthria	excellent	+++	5
6	M	40	13	13 (1)	R VOP	–	excellent	+++	3
7	F	36	14	3 (1)	R VOP	–	moderate	+	2, died of MS
8	F	28	9	2 (1)	L VOP	mild early paresis	good	++	5
9	F	62	18	2 (1)	L VOP	–	good	++	4, died of Ca
10	M	34	5	6 (1)	L VOP	–	excellent	+++	3
11	F	42	13	2 (1)	R VOP	mild early paresis	good	++	2

[1] Poor = no useful reduction in tremor = –; moderate = reduction in tremor to a degree that helped nurse the patient = +; good = reduction in tremore to allow patients to feed themselves and hold a cup of fluid = ++; excellent = reduction in tremor so patient can also write legibly = +++.

Discussion

Tremor is present in 59% of patients with clinically definite MS and is severely disabling in about 10% [12]. In MS, however, tremor may be accompanied by other components of ataxia including dysmetria, which, when they co-exist, may be difficult to distinguish.

There is very little information in the literature on the physiology of MS tremor [7]. However, Sabra and Hallett [13] studied 11 patients with MS with an alternating EMG burst pattern in upper limb agonist-antagonist muscle pairs and sub-divided the patterns on the basis of their movements into two groups: the first had low-amplitude tremor, with frequencies of between 5 and 8 Hz, which was only apparent on goal-directed movement. The second had disabling high-amplitude tremor, with lower frequencies of 2.5–4 Hz, which was present on posture and persisted or worsened on intention. Both types of tremor were accompanied by dysmetria [13].

Whilst thalamic surgery can effectively alleviate tremor, it may have little effect on other elements of ataxia. This may explain why thalamic surgery can alleviate other forms of tremor dramatically but has produced variable results in MS [14, 15]. Consequently, the distinction of tremor from other movement disorders in MS patients is important.

Eight of our 11 patients had involuntary movements whose spectral peaks were concentrated at one narrow frequency range, in keeping with a relatively pure tremor. These patients did well following stereotactic thalamotomy with an initial average reduction of nearly 80% in magnitude of their spectral peaks. In contrast, 3 of the 11 patients had multiple peaks in the spectra of their tracking movements, implying a more complex movement disorder. These patients were operated upon because on clinical grounds they had tremor, although spectra were collected and frequency analysis performed in an attempt to quantify this and to identify other movement disorders. Comparing pre- and postoperative spectra, it became apparent that, whilst thalamotomy could suppress a single component of a spectrum with well-defined frequency, it had little effect on the rest of the spectrum. Thus, spectral analysis in the frequency domain can characterise movement disorders in this way, as well as identify patients who are disabled, mainly with tremor, and determine who may benefit most from surgery. We suggest that this technique be incorporated into our patient assessment when selecting individuals for thalamotomy, which has less to offer to those patients who have complex movement disorders with multiple frequency peaks in their spectra. However, we speculate that pallidotomy or pallidal stimulation may be a more appropriate procedure for this group of patients. This concept is based on the similarity between the frequency spectra of the group 2 MS patients and those obtained from dyskinetic parkinsonian patients on *L*-dopa therapy [pers. obs. T.Z.A., P.G.B. and J.F.S.).

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