

Analysis of Action Tremor and Impaired Control of Movement Velocity in Multiple Sclerosis During Visually Guided Wrist-Tracking Tasks

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Summary: We investigated the relationship between action tremor (AT) and impaired control of movement velocity (MV) in visually guided tracking tasks, in normal subjects and in patients with multiple sclerosis (MS) with or without motor deficits. The effects of withdrawing visual feedback of either the target or the cursor were then investigated. Visually cued simple reaction times (SRTs) were also measured. The effects of thalamotomy on motor performance in these tasks were evaluated in seven patients. In the MS patients with tremor, there was no correlation between AT and impairment in control of MV, but the latter was highly correlated with an increased delay in SRT. Withdrawal of visually guiding cues increased the error significantly in MV, but reduced AT by ~30% in

magnitude. Frequency analysis indicated that the AT had two components: (a) non-visual-dependent, oscillatory movements, mainly at 4 Hz; and (2) visual-dependent, repetitive movements, with significant power at 1–2 Hz. Thalamotomy significantly reduced AT but hardly improved accuracy in MV. These results suggest that visual feedback of a spatial mismatch signal may provoke a visually dependent repetitive movement contributing to AT. Conduction delays along either the cortico-cerebello-cortical or the proprioceptive pathways and impaired working memory caused by MS may be responsible for the movement disorders in these patients. **Key Words:** Multiple sclerosis—Tremor—Movement velocity—Visual guidance—Tracking, wrist.

Many natural tasks involve movement of the hand to visual targets. In contrast to rapid preprogrammed movements, control of precise and slow goal-directed limb movements requires continuous on-line guidance based on knowledge of the current positions of the guiding target and of the moving limb. Visually guided tracking (VGT) tasks have thus proved useful in analyzing motor control strategies by, for example, suppression or delay of visual cues (1), forced pauses between movements (2), changes in tracking velocity (3) or changes in tracking trajectory (4). However, the relationships between voluntary movements made to track a visual target and movement disorders, such as tremor, remain uncertain. We therefore aimed to use simple manual tracking para-

digms to test the performance of visually guided movements by tremor patients.

By studying VGT tasks in monkeys (5) and in humans (6,7), several mechanisms underlying disturbances in the control of VGT have been addressed, including deficits in motor learning, motor memory, and the processing of visual and proprioceptive information. These deficits may be caused by broad visuomotor dysfunction following damage at neuronal stations, including primary and premotor cortices, cerebellum, and thalamus, or by damage to the nerve fibers connecting components of the cortico-cerebello-cortical control loop (8,9).

Tremor and a variety of other movement disorders such as tonic spasms, ballism, and palatal myoclonus caused by demyelinating lesions have been described in multiple sclerosis (MS) [for a recent review, see Tranchant et al. (10)]. Action tremor (AT; also called kinetic tremor, which occurs during movement and may become worse on intention) in MS therefore provides a pathological model for the study of visuomotor control. VGT

Received April 30, 1996; revision received October 1, 1996. Accepted January 15, 1997.

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tasks enabled us to assess AT and the associated impaired control in movement velocity (MV) simultaneously, so that the interaction between AT and visually guided movements could be investigated. Of course, the variable nature of MS unavoidably raises difficulties in interpreting changes in VGT when compared with lesions having either clearer pathogenesis or localization, such as Parkinson's disease (4) or cerebellar degeneration (7). We have tried to minimize these difficulties by restricting our observations to tremor and tracking movements within the VGT tasks that we have studied. We cannot yet extrapolate from these simple tracking tasks to more natural visually guided movements. Other rare movement disorders seen in MS are also beyond the scope of the present VGT tasks and are not addressed here.

MS patients with or without AT were therefore tested with VGT tasks and compared with normal controls. This enabled us to quantify tremor and voluntary movement simultaneously, with relatively simple experimental equipment. To address how visual guidance from the target or visual feedback of their own movement influences AT in MS during tracking, the visual guiding cues of tracking were selectively withdrawn. Delay in the initiation of movement, which may reflect delayed transmission because of demyelination in the visual or motor systems, was assessed by measuring visually cued simple reaction times (SRTs) with the same setup. Furthermore, we were able to make a preliminary assessment of the effects of thalamotomy, performed to reduce tremor and dystonia, on tracking performance.

METHODS

Patients with Multiple Sclerosis and Normal Controls

With local ethical committee approval, 22 MS patients were tested (14 women and eight men: age range, 21 to 51 years; average age, 38 years). Patients were either outpatients at the Department of Neurology or inpatients at the Department of Neurosurgery, Radcliffe Infirmary, Oxford. All had been diagnosed as having either clinically definite MS or laboratory-supported definite MS according to the MS classification of Poser et al. (11). They were also classified clinically as having either relapsing-remitting MS ($n = 14$) or secondary progressive MS ($n = 8$). Before testing, their eyesight was assessed by displaying both visual cues at a distance of 1 m, and one patient with severe sight deficits was excluded from the study; the patients who were included had neither nystagmus nor diplopia. Tracking performance of left and right hands was tested separately, and the results

were analyzed in terms of the number of hands rather than people. Data from each hand could be analyzed separately because:

1. Tracking movements of the two hands were tested separately, that is, VGT tasks were performed sequentially using one hand then the other, while the nontracking arm was relaxed.

2. Tracking movements were confined to the wrist. The subject's forearm was firmly held by an adjustable plastic channel fixed onto a chair; thus, there were limited possibilities for a simple mechanical linkage between the tremor observed in the tested hand and the contralateral hand.

3. MS plaques usually damage the motor system in a patchy fashion, and movement disorders in each hand are probably caused by independent plaques.

4. We found that tremor was statistically independent in the two hands. The standard deviation of MV (SD-MV) was used as an index of the severity of AT (see further on). The distribution of SD-MV was similar for both hands (Kolmogorov-Smirnov (K-S) two-variable test, $K = 0.32$ and $p > 0.1$), but values for each hand were not correlated ($r = 0.35$, $p = 0.14$, $n = 13$).

Since their AT was the primary measure to be focused on, the patients were divided into two groups based on observation of AT just before the tracking tests: (a) those with AT (*MS-tremor*, 26 hands in 15 patients), and (b) those without AT (*MS-no-tremor*, 14 hands in seven patients). Healthy subjects without neurological deficits (10 hands in five people; age range, 17–40 years) formed the normal control group. This allocation provided two kinds of control to compare with the MS-tremor group: MS-no-tremor patients and normal subjects. It enabled us to separate deficits due to nonspecific damage caused by the MS lesions and deficits due to specific lesions of the motor system.

Visually Guided Wrist-Tracking Task

A pursuit VGT task was used (Fig. 1). The target was a 12×12 -pixel hollow square displayed on a VGA computer screen. This target was initially stationary near one side of the screen; at the start of each trial, it moved horizontally at a constant speed to the other side of the screen and then stopped. Target velocities were 13.64° , 9.23° , 7.50° , and $5.50^\circ/s$, and were randomly allocated among 16 flexion movements, giving four trials at each target velocity. The subject held a low-resistance hand-held joystick allowing wrist flexion and extension, and the joystick position was displayed on screen as a 6×6 -pixel hollow-square cursor. The voltage signal generated by the joystick was amplified and digitally sampled

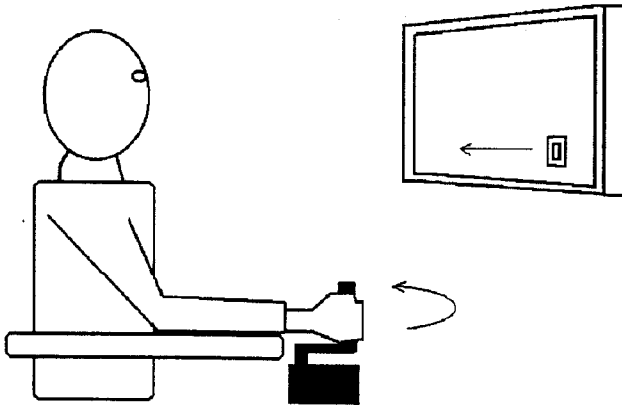


FIG. 1. The setup for wrist-tracking movement assessment. A computer screen displayed a cursor (a hollow square of 6×6 pixels) and a target (a hollow square of 12×12 pixels). The target was controlled by the computer and would move horizontally to left or right at four different velocities following a random sequence. Patients were instructed to rotate a low-friction joystick by a wrist flexion movement to keep the cursor at the center of the target whenever possible, and to move back to the starting position for next trial. The forearm was supported in an adjustable plastic channel set for each subject to hold the forearm firmly while allowing comfortable wrist flexion and extension over a range of 60° ($\pm 30^\circ$ around the neutral position).

with 12-bit resolution at 70 Hz. Data were stored on a personal computer for further analysis. The subject's forearm was supported in an adjustable plastic channel fixed to the arm of a chair, set for each subject to hold the forearm firmly while allowing comfortable wrist flexion and extension over a range of 60° ($\pm 30^\circ$ around the neutral position). Subjects was instructed to make a wrist flexion movement to keep the cursor inside or as near to the moving target as possible, and then to move back to the starting position with an unpaced extension movement for the next trial. The visual excursion of the target was in the range of 10° – 15° at the subjects' eyes, depending on the viewing distance to the display screen, which was set to be comfortable for each subject.

Visually Guided Tracking Tasks With and Without Visual Cues

Pursuit tracking was recorded under three conditions:

Task 1. Both cursor and target were displayed continuously so that visual comparison of target and cursor was possible.

Task 2. The target, but not the cursor, display was turned off for the second half of each trial. The subjects saw the target start each sweep, but as it reached the screen center, it was extinguished, reappearing in its final position 1 s after the end of each trial. The subjects were instructed to keep tracking the estimated position of target and had visual feedback of their own movement from the cursor, which remained visible throughout.

Task 3. The cursor display, but not the target display, was turned off for the second half of each trial. The subjects saw the cursor at the start of each sweep, but as the target reached the screen center, the cursor was extinguished, reappearing 1 s after the end of each trial. The subjects were instructed to track the continuously displayed target without visual feedback of the movement position.

Thus, for the second half of each trial in tasks 2 and 3, no visual information about the spatial relationship between the target and the cursor was available. Each subject was allowed a few practice trials on each task before recording began.

Visually Cued Simple Reaction Time Measurement

Reaction movements of the wrist were recorded following a visual cue given by a white square (now 20×20 pixels in size) jumping from side to side on the screen at random intervals of 2–4 s. Subjects were instructed to move the joystick as fast as possible by wrist flexion or extension when the target jumped, without worrying about the accuracy of movement. No visual feedback of wrist movement was displayed. Mean SRTs were calculated, averaged over 10 trials.

Analysis of Action Tremor and Movement Velocity

The wrist position signal was digitally differentiated and filtered with 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 subjects' initial reaction delay and acceleration phases. Similarly, for tasks 2 and 3, the selected data segments began 1 s after the target (task 2) or the cursor (task 3) was turned off. For the latter tasks, the data were compared with correspondingly timed segments from task 1. The computer then determined the target velocity, the mean MV, and the SD-MV for each of the 16 trials. Means and SDs over the 16 trials were then calculated for each measure.

We express the quality of the wrist tracking as the percentage mean velocity of the subjects' movement relative to that of the target; thus, perfect tracking would have a value of 100%. Impaired control of MV was reflected by the absolute percentage error in the MV (EV) relative to the target velocity.

The severity of AT was quantified by calculating the SD-MV; for perfect, smooth tracking, the SD of the MV would be zero. This measure is sensitive to the scatter of velocities around the mean tracking velocity and is thus analogous to measurement by accelerometry.

The frequency composition of the tracking records

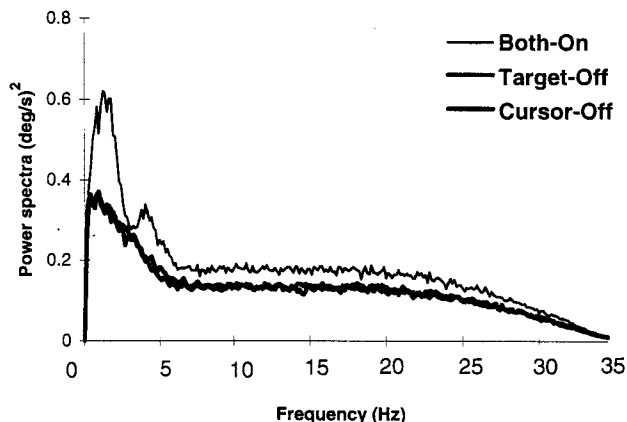


FIG. 2. Mean power spectra of tracking movements in the normal subjects. Tracking movement was intermittent when both the target and cursor were visible (*both-on*), with frequency components lying between at 0.5–3 Hz, peaking at 1.7 Hz. Depriving the subjects of visual feedback (*target-off* or *cursor-off*) greatly reduced the intermittent responses and led to smoother tracking. Data are presented as averages of spectra, 16 trials in each hand, 10 hands in five subjects.

was also computed. The same segments of the velocity records were used as just described, and the mean velocity was removed from each segment. The data were padded with zeros to provide 1,024 data points per segment, and a fast-Fourier transformation was calculated. Mean power spectra were calculated from the 16 trials per subject.

Stereotaxic Thalamotomy

Seven of the MS patients with secondary progressive MS who were suffering from persistent and disabling intention tremor (five cases) or dystonic posturing of the arm (two cases) underwent unilateral thalamotomy, in which thermocoagulative lesions were placed under stereotaxic guidance in the nucleus ventralis oralis posterior (Vop) of the thalamus. The thalamic target area was located during surgery by observing suppression of the kinetic tremor upon focal electrical stimulation. Visually guided wrist pursuit tracking was assessed in these seven patients 2 days before and between 1 and 4 weeks after surgery.

RESULTS

Visual Guidance and Intermittent Tracking Movements in Normal Subjects

In normal subjects, the tracking movements were typically intermittent (that is, discontinuous with small steps in the position of the wrist) rather than perfect, smooth pursuit. Hence, the velocity traces had numerous small peaks, and the calculated SD-MV was $6.36^\circ \pm 0.84^\circ/\text{s}$. However, their mean EV was only $1.25\% \pm 0.91\%$ (mean \pm SD, $n = 10$), very close to the ideal value of zero.

Frequency analysis revealed the typical band of frequency components (3) between 0.5 and 3 Hz, with a peak at 1.7 Hz (Fig. 2). Velocity errors significantly increased after withdrawal of visual guidance in tasks 2 and 3, when either the target or the cursor was turned off, to $6.26\% \pm 4.96\%$ and $9.33\% \pm 8.32\%$, respectively. These were significantly higher than the mean EVs in task 1 ($p < 0.006$, Student's *t* test, $n = 10$). However, depriving the subjects of visual guidance (target or cursor withdrawn) also led to smoother tracking, even if positional accuracy was reduced. Thus, the measure of intermittence (SD-MV) fell significantly to $5.75^\circ \pm 1.14^\circ/\text{s}$ ($p = 0.006$) and $5.89^\circ \pm 1.02^\circ/\text{s}$ ($p = 0.026$), respectively. The frequency range of the main spectral components remained unchanged (Fig. 2), but the peak at 1.7 Hz was reduced.

Analysis of Tracking Performance in Patients with Multiple Sclerosis

The MS patients were classed as MS-no-tremor and MS-tremor, based on clinical observation of the tremor before the tracking tests. SD-MV, EV, and SRT were compared between the normal controls and these two groups of MS patients (Table 1). For all comparisons, there were no significant differences between the performance of the MS-no-tremor group and that of the controls, but there were highly significant differences between these two groups and the MS-tremor group.

Underlying purposeful tracking movement with AT superimposed could nevertheless be seen in the tracking records of 14 of the 15 patients grouped as MS-tremor, on which AT was superimposed. Figure 3 shows a typical record. The SD-MV average score was significantly elevated in the MS-tremor group, as expected, since SD-MV is an index of tremor. This group also had significantly increased error in relative tracking velocity (EV)

TABLE 1. Comparison of SD-MV, EV, and SRT in normal controls and MS patients

	SD-MV ($^\circ/\text{s}$)	EV (%)	SRT (s)
Controls	6.36 ± 0.84 $n = 10$	1.25 ± 0.91 $n = 10$	0.20 ± 0.02 $n = 10$
MS-no-tremor	6.81 ± 1.64 $n = 14$	1.20 ± 0.70 $n = 14$	0.22 ± 0.03 $n = 14$
MS-tremor	68.76 ± 85.60 $n = 26$	16.42 ± 15.93 $n = 26$	0.33 ± 0.11 $n = 18$
Single-factor ANOVA	$p = 4.14 \times 10^{-3}$	$p = 6.82 \times 10^{-5}$	$p = 5.19 \times 10^{-5}$

Data are presented as mean \pm SD. ANOVA, analysis of variance; EV, error in the movement velocity; MS, multiple sclerosis; SD-MV, standard deviation of the movement velocity; SRT, simple reaction time.

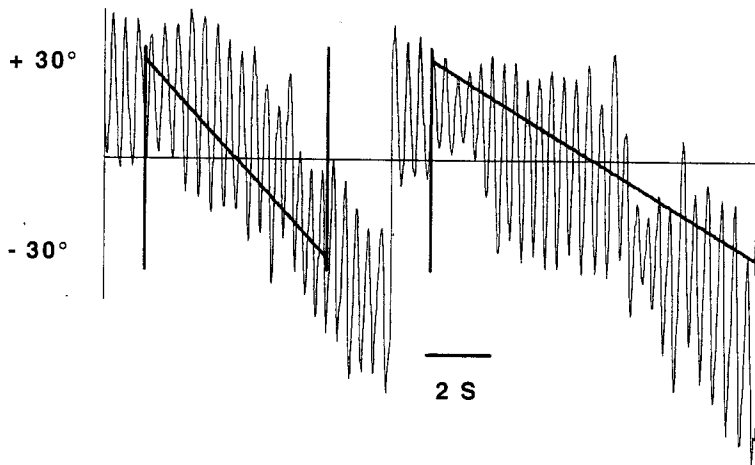


FIG. 3. A typical record of two sequential trials of tracking at different velocities in a patient with multiple sclerosis who had severe action tremor. The movement of joystick (*thin line*) is superimposed on the track of a moving target (*heavy line*). The unit bar indicates a 2-s period.

compared with the other two groups (Table 1). Considering the mean tracking velocity from each hand tested as a percentage of the target velocity (that is, the unsigned error in tracking velocity averaged from the 16 trials), the MS-tremor group displayed large constant errors in MV. Relative to the target velocity, the majority of hand records displayed a reduced mean velocity calculated across the 16 trials ($82.19\% \pm 17.60\%$, $n = 19$), with relatively few showing an excessive mean velocity ($112.67\% \pm 10.25\%$, $n = 7$). SRT was significantly prolonged in the MS-tremor group compared with the other subject groups ($p < 0.0001$). Importantly, however, there was neither a significant correlation between the severity of AT and EV in this group of patients ($r = 0.14$, $p =$

0.48 , $n = 26$ hands) nor one between the severity of AT and SRT ($r = 0.17$, $p = 0.50$, $n = 18$). In contrast, EV significantly correlated with prolongation of SRT ($r = 0.56$, $p = 0.015$, $n = 18$).

Effect of Withdrawing Visual Cues on Tracking of Multiple Sclerosis

Withdrawal of either the cursor cue or the target cue significantly increased the EV in both groups of MS patients with and without AT compared with normal subjects (Fig. 4). Thus, both patient groups appear to be more dependent on visual cues to maintain accurate tracking. Furthermore, when either visual tracking cue was removed, there was significant suppression of the

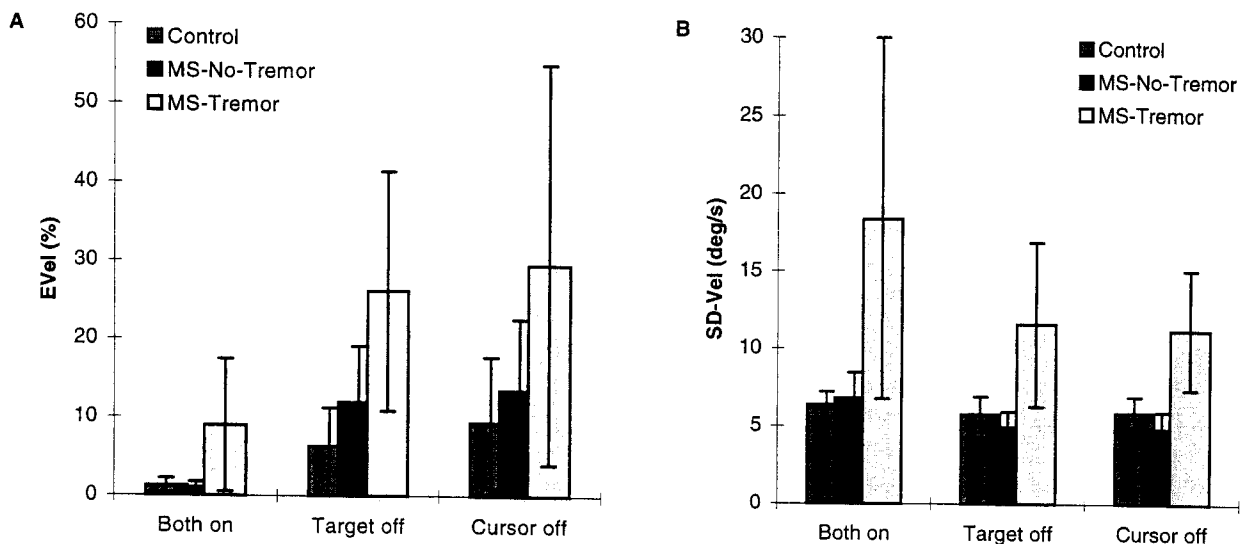


FIG. 4. A: Increase in percentage error in the movement velocity (EV; mean \pm SD) induced by withdrawal of either the target cue or the movement cue was more pronounced in patients with multiple sclerosis (*MS-no-tremor* and *MS-tremor*; $p < 0.05$, two-factor analysis of variance, $n = 13$) compared with normal subjects (*controls*, $n = 10$). B: Magnitude of the action tremor (standard deviation of the movement velocity, *SD-MV*; mean \pm SD) in MS patients with tremor (*MS-tremor*) was significantly reduced by withdrawal of either visual cue ($p < 0.05$, two-factor analysis of variance).

SD-MV to ~70% of its original value, in both the MS-no-tremor and the MS-tremor groups, with a significant correlation of tremor scores between the target-off and cursor-off conditions ($r = 0.92$ and $r = 0.99$, respectively).

Examination of the power spectra of the tracking movements revealed that the MS velocity records consisted of two major components with differences in their frequency range and their dependence on the visual cues. First, there was a band of frequencies with a peak at 4 Hz that were unaffected by withdrawal of the target (T-off; Fig. 5) or cursor (C-off; Fig. 5), that reflected non-visual-dependent oscillatory movements. Second, there was a band of frequencies that reflected visually dependent repetitive movements, as revealed by the differences between the both-on spectrum and either the T-off or C-off spectra in Fig. 5. For the lower end of this frequency band (1–2 Hz), there was a statistically significant reduction in power when visual cues were removed in tasks 2 and 3 ($p < 0.05$, unpaired t test, $n = 12$). The upper frequency band (3–7 Hz) did not significantly differ between the same conditions.

Effects of Thalamotomy on Action Tremor

In seven patients, unilateral thalamotomy was performed by placing a lesion in the Vop nucleus of the thalamus. Comparing the mean AT and MV values obtained before and after the operation within this group, the AT was significantly reduced ($p = 0.022$, paired t test), whereas the velocity of the patients' voluntary wrist movements was affected variably (Fig. 6). Errors in the

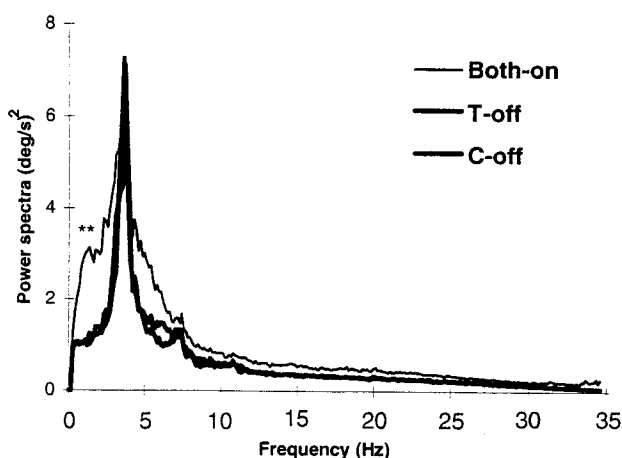


FIG. 5. Averaged power spectra from tracking with both the movement cursor cue and the target cue being displayed (*both-on*), target cue (*T-off*) or movement cursor (*C-off*) being turned off, in 12 hands. The frequency of the action tremor (AT) ranges from 2 to 6 Hz, with a sharp peak at 4 Hz. The T-off and C-off traces are significantly reduced in power compared with the both-on trace at the frequency range of 1–2 Hz. Data are presented as mean values; * $p < 0.05$, unpaired t test.

mean velocity were reduced in four of seven patients, but increased slightly in the remaining three.

DISCUSSION

We have examined AT and its relationship with impaired control of MV in patients with MS by using VGT tasks. First, the AT of these patients was found to be more pronounced in the presence of visual cues, because AT was significantly reduced by withdrawal of these cues. Second, the severity of tremor was independent of delayed reaction time, and independent of the accuracy of tracking velocity. However, we found that simple visual reaction times did correlate with errors in tracking velocity. Third, thalamotomy appears to reduce AT greatly, but had variable effects on EV.

Perhaps the most intriguing result we observed was that the tracking movements recorded in the tremor patients appear to have both visually dependent and independent components. Frequency analysis of the velocity records indicated that the power spectra had two major frequency bands with different visual dependence: (a) visually independent oscillatory movements predominantly at 4 Hz; and (b) visually dependent, repetitive components, with power between 1 and 2 Hz, which were significantly reduced when the visual cues were withdrawn.

An explanation for the visually dependent component of tremor can thus be proposed, based on the present results and on previous findings (3) in normal human VGT movements. In normal subjects, pursuit tracking tends to be intermittent. This intermittence depends on visual feedback, and the subjects make discrete error corrections each time the tracking error exceeds a given threshold. The spectral power of these responses peaks at 1–2 Hz and can be reduced by depriving the subjects of visual feedback of their movement (3); these intermittent corrections can also be delayed by delaying visual feedback (1).

In the present study, the frequency band of the visually dependent component of the tremor (that is, that which was significantly reduced when feedback of visual cues was removed) corresponds to that of the intermittence in normal tracking movement. This visually dependent component was significantly larger in the patients with AT than in the other two groups. These components are therefore provoked by the visual feedback signal of excessive movement error, the spatial mismatch between the target and the cursor. To assess this spatial mismatch requires simultaneous display of both visual cues on the screen, one which serves as a reference to the other. The visual error signal was of course greatly enhanced in the AT patients because the cursor's position reflected their

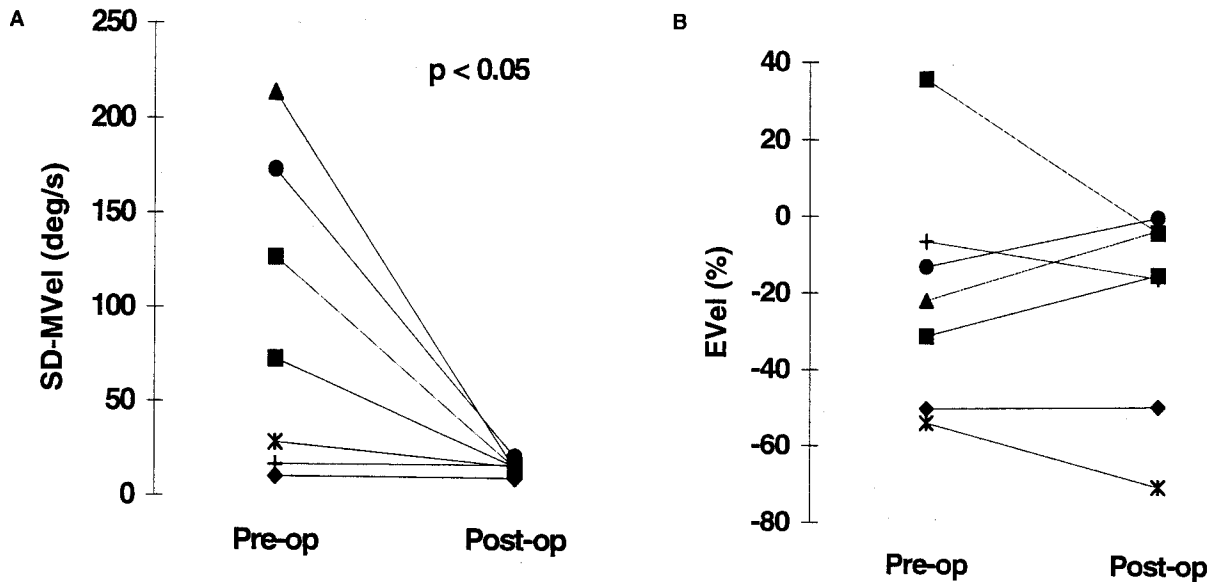


FIG. 6. Effects of thalamotomy on action tremor (AT) and impaired control of movement velocity (MV) in the contralateral hand of the patients with multiple sclerosis. As a group, the AT (A) was significantly reduced ($p < 0.05$, paired t test) by the thalamotomy, whereas EV was not (B). Data from seven individuals are presented.

tremor. The mismatch signal can be withdrawn by turning off either the target cue or the movement cue, and this in turn smooths their tracking but increases their errors.

The prolongation of SRT and the errors in MV indicate that delayed initiation and impairment in control of MV coexisted in these MS patients. More interestingly, the prolongation of SRT significantly correlated with the magnitude of the EV, which suggests that control of both initiation and velocity of a movement may share a common segment of the motor control circuit. One obvious candidate is the cortico-cerebello-cortical loop by which motor commands are projected from the motor cortex via the cortico-ponto-cerebellar pathway to the cerebellum, and return via the cerebello-thalamo-cortical pathway back to the motor cortex. Evidence suggests that this motor control loop is responsible for aspects of the planning, initiation, and execution of movement, including the maintenance of constant velocity and force (12,13).

In addition, our data suggest that the MS patients have an increased dependence on visual cues, since there was a significant increase in velocity error when the visual cursors were blanked. Whether this increased dependence on visual input is due to a deficit in proprioceptive inputs, analogous to a peripheral sensory neuropathy (2), or to a cerebellar dysfunction in processing sensory afferents (14) cannot be definitely decided without a detailed assessment of the status of their proprioceptive afferents. However, this dependence on visual inputs was

clear both in the MS-tremor and in the MS-no-tremor groups, suggesting that it is not related to their motor performance in a straightforward way.

In contrast to previous investigations (14,15), we found that withdrawal of the target cue in MS patients had a similar effect as withdrawal of the movement cursor, both significantly increasing the error in MV compared with normals. This was not the case in patients with "pure" cerebellar lesions (14). A possible explanation is that there may be a reduction in the working capacity of short-term motor memory, namely, in the patients' mental model of the external environment. Such a working memory is required to predict target position and velocity after the target cue has been blanked. During that period, updated information about the target position and velocity cannot be gained from the current visual input, but must be based on information acquired during the first half of each trial and processed by motor memory. The fact that withdrawal of the movement cursor cue also significantly reduced tracking accuracy in these MS patients implies that not only are they dependent on visual information of the target, but their internal representation of limb position and velocity, presumed to be generated by an internal model in the cerebellum (16), has been undermined as well.

AT and impaired MV control in MS are caused by damage to the motor control loops due to the demyelinating lesions. However, we have shown that they do not parallel each other in all cases. In fact, there was no correlation between the severity of the two, and they

appear to respond to thalamotomy differentially. It is likely, therefore, that other factors are important. We speculate that tremor may be generated within a closed motor control loop. The initial conduction delays caused by the demyelinating lesions may then shift the frequency of impulse transmission around this loop so that it falls into a fairly narrow frequency band at which resonance with central oscillators is set up. Such resonating signals would lead to generation of tremor. Thus, in an individual patient a particular increase in loop delay could lead to pronounced tremor as the control loop resonates, whereas in another patient a somewhat greater delay could lead to a pronounced impairment in kinematic control of movement, but not to resonant oscillations and then tremor. Thus, there could be severe delay (leading to poor velocity control and increased reaction times) with little tremor, or with severe tremor but relatively little increase in delays.

It is interesting to ask why lesions in the Vop nucleus of the thalamus diminish AT but do not improve control of MV in these MS patients; there is no clear answer yet, although the resonance mechanism just proposed may provide a clue. Intraoperative electrical stimulation or permanent thermocoagulating certainly will not restore the initial delayed conduction that is caused by demyelination. These procedures may, however, abolish the resonance within the control loop by further perturbing the transmission of motor signals around the loop. We speculate that this could then shift the oscillations beyond the particular resonant frequency band and lead to a reduction in the excessive drive to motor neurons. Thus, thalamotomy could reduce tremor while having quite varied positive or negative effects on voluntary movement.

Acknowledgment: We are very grateful to the patients and normal subjects for their cooperation, and to Miss Helen Miles for her help with recruiting MS patients. We also thank the

McDonnell-Pew and MRC Centres for Cognitive Neuroscience, Oxford. R.C.M. and X.L. are supported by the Wellcome Trust.

REFERENCES

1. Weir DJ, Stein JF, Miall RC. Cues and control strategies in visually guided tracking. *J Mot Behav* 1989;21:185-204.
2. Miall RC, Haggard PN, Cole JD. Evidence of a limited visuo-motor memory used in programming wrist movements. *Exp Brain Res* 1995;107:267-280.
3. Miall RC, Weir DJ, Stein JF. Intermittent responses in human manual tracking. *J Mot Behav* 1993;25:53-63.
4. Johnson MTV, Kipnis AN, Coltz JD, et al. Effects of levodopa and viscosity on the velocity and accuracy of visually guided tracking in Parkinson's disease. *Brain* 1996;119:801-813.
5. Miall RC, Weir DJ, Stein JF. Visuo-motor tracking during reversible inactivation of the cerebellum. *Exp Brain Res* 1987;65:455-464.
6. Beppu H, Suda M, Tanaka R. Analysis of cerebellar motor disorders by visually guided elbow tracking movement. *Brain* 1984; 107:787-809.
7. Beppu H, Nagaoka M, Tanaka R. Analysis of cerebellar motor disorders by visually guided elbow tracking movement. 2. Contribution of the visual cues on slow ramp pursuit. *Brain* 1987;110: 1-18.
8. Stein JF. Role of the cerebellum in the visual guidance of movement. *Nature* 1986;232:217-221.
9. Horne MK, Butler EG. The role of the cerebello-thalamo-cortical pathway in skilled movement. *Prog Neurobiol* 1995;46:199-213.
10. Tranchant C, Bhatia KP, Marsden CD. Movement disorders in multiple sclerosis. *Mov Disord* 1995;10:418-423.
11. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227-231.
12. Diener H-C, Dichgans J. Pathophysiology of cerebellar ataxia. *Mov Disord* 1992;2:95-109.
13. Houk JC, Keifer J, Barto AG. Distributed motor commands in the limb premotor network. *Trends Neurosci* 1993;16:27-32.
14. Cody FWJ, Lövgreen B, Schady W. Increased dependence upon visual information of movement performance during visuo-motor tracking in cerebellar disorders. *Electroencephalogr Clin Neurophysiol* 1993;89:399-407.
15. Haggard P, Miall RC, Wade D, et al. Damage to cerebello-cortical pathways after closed head injury: a behavioral and magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* 1995;58: 433-438.
16. Miall RC, Weir DJ, Wolpert DM, Stein JF. Is the cerebellum a Smith predictor? *J Mot Behav* 1993;25:203-216.