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Visuomotor Performance in Patients With Essential Tremor

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Summary: Essential tremor (ET) is the most prevalent extrapyramidal disorder, yet its diagnosis is still controversial. This article introduces new findings that pertain to this diagnostic problem. Twenty-three patients with ET were studied. Patients with parkinsonism, cerebellar signs, severe head injury, or those under neuroleptic medication were excluded. Twenty-five normal subjects served as control subjects. Visuomotor tests involving tracking and tracing along three different paths with both the right and left hands, were used. Performance was assessed by measuring test duration, directional error, the proportion of the cumulative test time during which directional error exceeded half the maximal possible level (PT50%), the mean distance from the model path, the velocity of the hand movement, and the number of tracking interruptions. In 15 of 23 patients performance was the same as in the control subjects. These patients were defined as having a "simple condition" of ET (ETs). Considerable visuomotor impairment was found in eight patients who were regarded as having a "complex condition" of ET (ETc). Patients with ETc had significantly lower tracking speed, more tracking interruptions, longer test duration, greater directional error, greater PT50%, and greater distance from path than patients with ETs or control subjects. Most patients with ET appear to have normal visuomotor capabilities (ETs) but some display significant visuomotor disturbances (ETc). Considering the presence of similar impairments in patients with early Parkinson's disease and the increased prevalence of parkinsonism in patients with ET, it is possible that preclinical parkinsonism exists in patients with ETc. Further follow up of patients with ETc is necessary to verify this possibility. **Key Words:** Essential tremor—Visuomotor control—Parkinson's disease.

Essential tremor (ET) is a common autosomal-dominant disease with a peak incidence at the second and sixth decades. Tremor is usually manifested in the hands (approximately 90% of all cases), but the head, voice, legs, and chin may also be affected. Tremor is seen when the arms are stretched out horizontally (postural tremor) and/or during movement (action tremor). Some tremor may occur in neurologically healthy individuals but is considered to be pathologic only when interference with normal motor functions becomes disabling.[1] There is no specific test or biologic marker for ET and its diagnosis is controversial.[1–4]

Imaging studies have linked ET with activity changes in the cerebellum and red nucleus.[5–7] Electrical stimulation in the ventral-intermediate thalamus was found to alleviate this condition.[8] In addition, a lesion of a thalamic region where neuronal activity correlated with tremor was found to provide effective relief.[9] Thus, ET is found to be linked with changes in specific motor pathways with no gross pathology.

From a functional point of view, it is not clear whether ET derives from poor control of ongoing movements (including posture) or whether it is caused by independent postural oscillations superimposed on the currently executed motor act.

The present work attempts to shed some light on this problem by trying to assess the degree to which various aspects of visually guided movements are influenced by tremor.

METHODS

Subjects

Twenty-three patients with ET were studied. Mean age of the patients was 54.2 ± 4.1 years (mean ± standard error). All patients were diagnosed as having ET on the basis of having postural tremor of the hands and kinetic tremor during feeding, drinking, and/or writing in at least

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one hand. Duration of tremor was 18 months in one patient, 3 years in two patients, 5 years in three patients, and between 8 and 50 years in the remaining 16 patients. Familial history was not considered to be a diagnostic factor of ET. Signs of parkinsonism (that is, rest tremor, rigidity, bradykinesia, gait disturbances) served as exclusion criteria. Other exclusion criteria included neuroleptic treatment, alcoholism, cerebellar signs, and severe head injury. The diagnostic criteria used in this study for the diagnosis of ET are in agreement with those published in Table 1 of the article by Louis et al.[4] No ET-related treatment was given to any of the patients at the time of the study.

Performance of the patients was compared with that of 25 control subjects with a mean age of 57.1 ± 1.7 years.

Instrumentation

All visuomotor tests (VMT) were done with a computerized system, consisting of a digitizing tablet, a mechanically supported manipulandum containing the digitizer's stylus and a computer monitor. The digitizing tablet was placed horizontally and was hidden from the subject's view by an overlying board fixed 15 cm above the tablet. The computer monitor was placed on top of the overlying board at eye level and was used to display paths for tracing and tracking.[10] A screen cursor represented the location of the unseen manipulandum which could be moved freely across the digitizer's surface. A one-to-one correspondence between movements of the manipulandum and movements of the screen cursor was maintained. The location of the manipulandum was read by the computer at 100 Hz with a resolution of 0.05 mm.

Tests

Tracing

A path (see below) and a cursor were displayed on the screen. The subject was asked to bring the cursor to a designated starting point from which he or she moved it along the entire path at a self-determined pace as accurately as possible by use of the unseen manipulandum.

Tracking

The same path was used. A 1-cm target circle was programmed to move along the path at a predetermined speed of 22 mm/sec. The subject was asked to maintain the cursor within the moving target by moving the manipulandum correspondingly. In case of failure to keep the cursor within the target, the latter stopped moving (tracking interruption) until the cursor entered it again.

Paths

Three path types (sine-wave, square, and circle) were used. This choice of paths ensured a wide range of task difficulties, from simple straight movements (square path) through a constant change in direction (circular path) to a variable change in direction (sine-wave path). All three path types were used with each hand in tracing and in tracking. The VMT results (see below) are given as grand averages across all path types.

Scores

Performance was evaluated off-line by use of the following measures.

1: The total time (TT) of test performance.
2: Directional error (DirEr). An instantaneous directional error was computed at each point along the sampled hand trajectory. It consisted of the movement vector component pointing in a direction perpendicular to the model path divided by the total movement vector. A zero directional error means that movement proceeded parallel to the model path. A directional error of 1 indicates that movement was perpendicular to the model path. The instantaneous DirEr values were averaged along each path. Note that the DirEr reflects only the relative direction of hand movement independently of the distance from the model path.
3: The proportion of cumulative test time during which the directional error was greater than 0.5 (PT50%). The cumulative test time during which movement advanced away or toward the model path rather than along it was computed and factored by the total test time. The PT50% is a more robust measure of directional control than the mean directional error because it is less sensitive to occasional deviations from the model path and because it gives more weight to the ongoing performance of the subject.
4: Mean distance from the model path (MnDist).
5: Velocity of hand movement (V).
6: Number of tracking interruptions (NInts).

Test Procedure

Each subject was tested on tracking of the sine-wave path with the right hand and then with the left hand, followed by tracing of that path with each hand. The same sequence was repeated using the square path and then, again, with the circular path. Before testing began, each subject received an acquaintance trial of tracking along a straight line. The entire testing session took 15–30 minutes.

RESULTS

Most patients with ET (15 of 23) were able to perform the VMT with the same proficiency that characterized the control subjects. Some patients (eight of 23) showed considerable impairment. In all patients, performance

was not affected by tremor because tremor minimized during testing, and because the patients were able to stabilize the manipulandum by letting the fingers and wrist absorb most of the remaining involuntary movements. The absence of tremulous movements from the tracking and tracing trajectories of two patients with ET can be seen in Figure 1. The upper part of this figure shows the performance of a 53-year-old patient with ET with no visuomotor dysfunction in either tracking (top) or tracing (bottom) of the sine-wave path. The lower part of Figure 1 shows the performance of a 54-year-old patient with ET who experienced considerable difficulty in the same tasks. Although this patient had 62 tracking interruptions, it can be seen that they were primarily the result of slowed movement (14 mm/sec compared with 18 mm/sec of the other patient) rather than to tremor. The difference between the two patients is even more conspicuous in tracing. Here, the first patient was able to complete the sine-wave tracing within 18.9 seconds, of which only 2.4 seconds included movement with DirEr >50% (PT50% = 12.7). In contrast, the second patient was able to trace less than half of the model path within the allotted 64.5 seconds and had a PT50% of 41.9. This poor tracing performance was the result of severe impairment in control of movement direction together with marked slowness, but not to a presence of tremor.

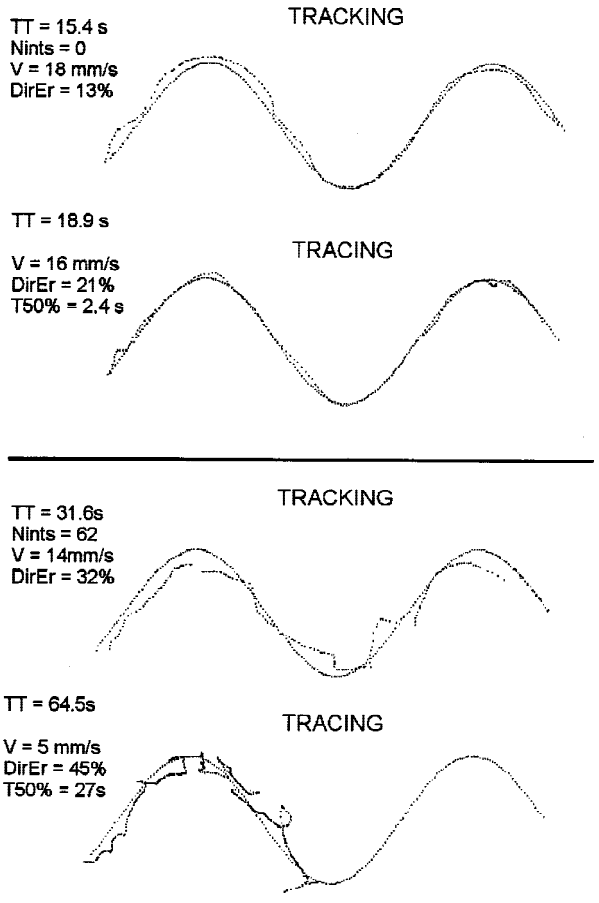

FIG. 1. Performance of a patient with ET who has no visuomotor deficit (top part) and a patient with ET who has visuomotor impairment (bottom part).

Between-Hands Differences

In most patients, tremor was more accentuated on one side of the body. Nevertheless, the VMT revealed symmetric performance of both hands, as shown in Figure 2. The top part of Figure 2 shows the mean tracking time of the left hand (Y-axis) as a function of the mean tracking time of the right hand (X-axis). It can be seen that the control subjects and most patients with ET cluster on the diagonal near the graph's origin. The mean tracking time of eight patients with ET was more than 3 standard error units greater than the control's mean during performance with either the right or left hand. These patients are denoted by solid triangles.

The middle part of Figure 2 shows the hand-dependent number of tracking interruptions, a critical measure of tracking persistence. This part again shows the between-hands similarity of all subjects and the clustering of most patients with ET with the control subjects. The same eight patients with prolonged tracking times can be seen to have a much higher number of tracking interruptions, symmetrically, in both hands.

The bottom part of Figure 2 shows the hand-dependent PT50% in tracing. This robust measure of directional control again shows a strong between-hands symmetry in all groups of subjects. In addition, it shows that seven of the eight patients with prolonged tracking times also had significantly impaired directional control.

Of the 23 patients with ET, 15 had normal visuomotor performance and were thus regarded as patients with a simple condition of essential tremor (ETs). The other eight were found to have abnormal visuomotor performance in addition to essential tremor and were considered to present a complex condition of essential tremor (ETc).

Comparisons Between Patients and Control Subjects

A comparison between group means of the control subjects, patients with ETs, and those with ETc is shown in Figure 3. The top left part of this figure shows that tracking speed of patients with ETs was the same as the control subjects, whereas patients with ETc had a significantly lower tracking speed (comparison between ETs and ETc: $t = 2.7$, $p = 0.03$). The mean number of tracking interruptions was almost identical in control

subjects and patients with ETs (middle part of Figure 3), but was nearly an order of magnitude greater in patients with ETc (comparison between ETs and ETc: $t = 6.44$, $p = 0.0002$). Finally, the control subjects and patients with ETs had similar mean tracking times (top right) which were almost threefold shorter than those of patients with ETc (comparison between ETs and ETc: $t = 4.26$, $p = 0.004$).

The lower two parts of Figure 3 compare the ability of all subjects to control movement direction and to approximate the model path during tracing. The left part shows that the mean PT50% of patients with ETs was similar to control subjects whereas that of patients with ETc was almost three times greater ($t = 4.28$, $p = 0.002$). The lower right part shows that the mean distance from path (MnDist) of patients with ETs grouped with the control subjects, whereas that of patients with ETc was much greater ($t = 4.25$, $p = 0.002$).

DISCUSSION

The main finding of this study is that patients with essential tremor can be divided according to whether they have normal or reduced visuomotor capabilities. Therefore, the discussion will focus on the relation between essential tremor and visuomotor control and on a possible explanation for the existence of two distinct groups within the population of patients with ET.

Visuomotor Control and Essential Tremor

First and foremost, our findings demonstrate that normal visuomotor capabilities may coexist with a condition of essential tremor. This means that the neuronal mechanisms that produce tremor are distinct from those that support visuomotor coordination. We should point out that the patients with ET who were studied were selected because of absence of rest tremor. Minimization of their postural/action tremor during task performance, in most cases down to a complete absence, reflects this fact, because the VMT task was performed with a well-supported hand using slow movements. In fact, most patients had tremor while approaching the manipulandum, but this tremor subsided once the hand was rested comfortably on it.

Several studies indicate that ET involves the cerebellar cortex[5–7] and the red nucleus,[5,7] but other brain structures are also implicated.[5] Of these, the thalamus appears to be of special importance. Hua et al.[9] have shown, by spectral cross correlation analysis, that thalamic activity is linearly related to forearm electromyographic activity during tremor. Ablation of the pertinent thalamic region was found to relieve tremor. In another study, Alesch et al.[8] have reported a series of parkinsonian patients and

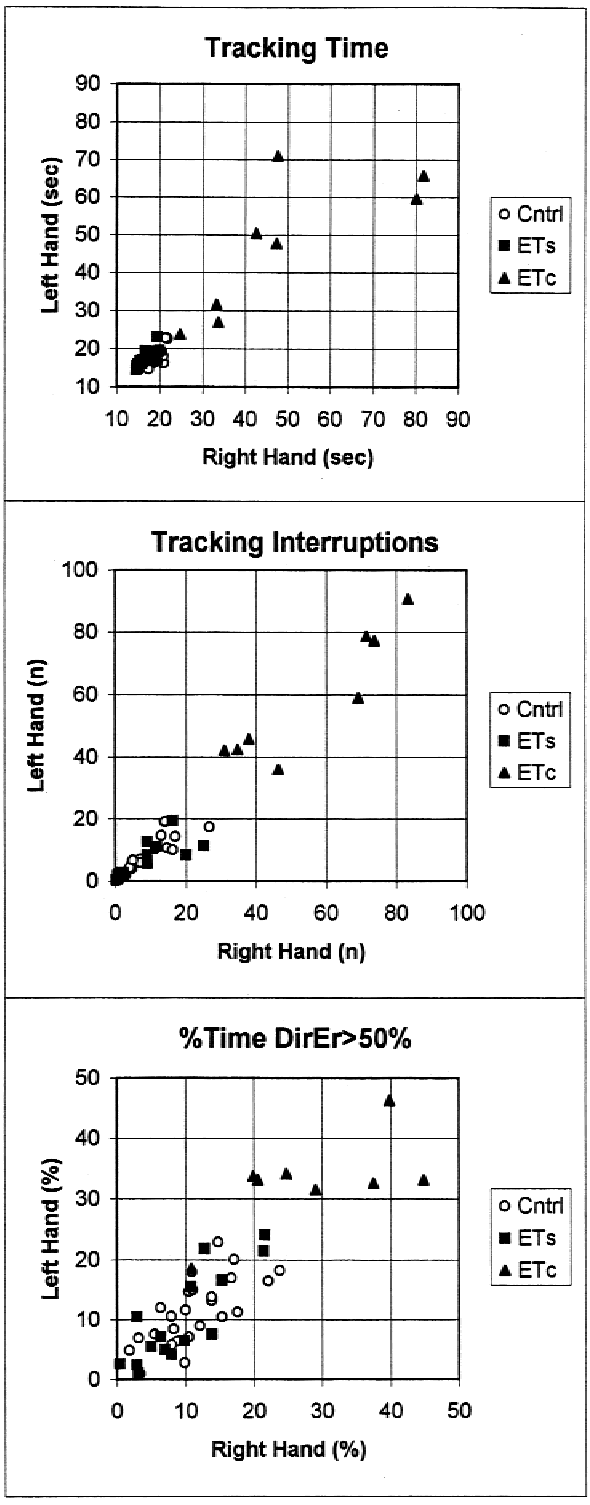

FIG. 2. Comparison between visuomotor performance of the right (X-axis) and left (Y-axis) hand of all patients with ET and control subjects. Each plot pertains to a separate measure of performance as stated by the plot's title. Open circles, control subjects; filled squares, patients with ET who have no visuomotor deficit (ETs); filled triangles, patients with ET who have a visuomotor deficit (ETc).

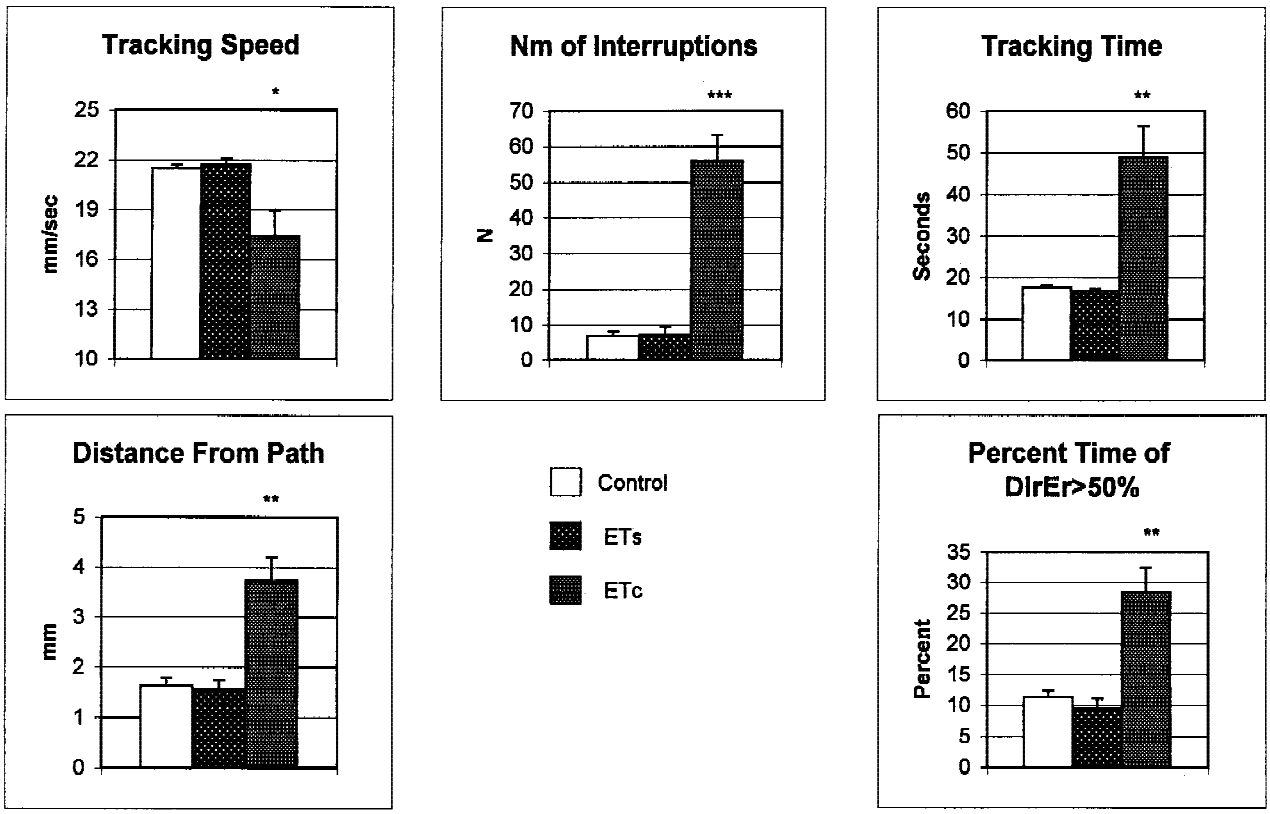

FIG. 3. Comparison between performance of control subjects (open columns), patients with ETs (dotted columns), and patients with ETc (gray columns). Vertical bars = +1 standard error unit. *T* test comparison between patients with ETs and those with ETc: *p <0.05, **p <0.005, ***p <0.0005.

patients with ET in whom tremor was alleviated chronically by chronic electrical stimulation of the ventral intermediate thalamic nuclei.

The cerebellum was found to be activated during visually guided tracking and was concluded to be specialized for using sensory information to correct movements.[11] Our findings indicate that this function may remain intact in ET. Therefore, we propose that the cerebellar involvement in visuomotor control does not overlap its role in the control of tremor.

In patients with Parkinson's disease (PD) too, alleviation of tremor by thalamic stimulation was reported not to affect other signs of parkinsonism.[8] Therefore, it seems that in both disease conditions, tremor is caused by changes in limb-stabilizing mechanisms that differ from the circuitry through which specific movements are controlled. In this context, it is worthwhile to note the low correlation between different types of tremor, for example, postural tremor versus writing tremor.[12] It is possible that limb stabilization involves a number of neuronal circuits that apply to different functional situations as well as to different body parts. It seems that none of these circuits is necessarily involved in visually guided arm movements.

Essential Tremor and Parkinsonism

Many studies have demonstrated that the basal ganglia play an important role in visuomotor coordination.[13–16] Our own studies[10,17] have demonstrated deficient directional and velocity control in parkinsonian patients, similar to those found in the group of patients with ETc. A condition of early parkinsonism in the patients with ETc can explain the present findings but apparently contradicts the lack of a clinical diagnosis of parkinsonism in these patients. Two arguments can support the possibility that parkinsonism is present in patients with ETc. First, increased prevalence of PD has been reported in patients with ET.[18,19] This means that the occurrence of patients with both ET and PD should be expected at a higher rate than predicted by the prevalence of PD in the general population. Second, similar visuomotor deficits were demonstrated in the asymptomatic hand of patients with unilateral PD,[17] showing that visuomotor testing is more

sensitive to basal ganglia dysfunction than standard clinical examinations.

The disagreement associated with the diagnosis of ET[2–4] may result in part from the coexistence of two distinct disorders in the same patient. Koller and Montgomery[3] have concluded that the clinical diagnosis of PD is most difficult early in the disease when the signs and symptoms are most subtle. These authors suggested ET as one of a possible alternative differential diagnoses. Given that ET and PD are not mutually exclusive, it appears that their coexistence in the same patient produces a clinical picture that is identified in this article as complex essential tremor.

Another possibility to resolve the lack of a PD diagnosis in patients with ETc is by hypothesizing that the visuomotor impairment in ETc results from a separate pathology which differs from the one underlying Parkinson's disease. This would make up an as-yet undescribed ET-related symptomatology.

The conflict between the two possible explanations can be resolved by long-term follow up of the patients with ETc. While this is beyond the scope of this article, an indication that the first alternative is more plausible comes from obtaining initial positive response of some patients with ETc to antiparkinsonian treatment. Still, conclusive evidence on whether ETc represents patients with preclinical parkinsonism or whether it is another complication associated with essential tremor must await further studies.

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