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Motor Initiation and Execution in Essential Tremor and Parkinson's Disease

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Summary: Clinical differentiation of essential tremor (ET) from idiopathic Parkinson's disease (iPD) is based on the lack of akinesia and bradykinesia. Nevertheless, early tremor-predominant iPD often is difficult to distinguish from ET. Motor initiation and execution in ET, iPD, and normal control (NC) subjects were investigated. Individuals with iPD, ET and NC performed a reaction-time wrist flexion and extension task. Motor performances were similar between ET and iPD and both were different than normal control subjects. Both the patients with iPD and ET had longer reaction times and slower movement velocities than NC subjects. This may help to explain some of the difficulties in distinguishing patients with these two diseases. The similarities of motor performance suggest that while ET and iPD may be separate disease entities, they may share similar pathogenic motor mechanisms from the perspective of an integrated motor system that drives the motor cortex. **Key Words:** Parkinson's disease—Essential tremor—Reaction times—Movement velocity—Pathophysiology.

Controversy exists as to whether there is a causal relationship between idiopathic Parkinson's disease (iPD) and essential tremor (ET)[1–4]; for example, does having ET increase the risk of having iPD. Clinically, patients with ET and tremor-predominant iPD may have similar clinical manifestations. The typical tremor of iPD occurs at rest but may be present with sustained posture and with action. The typical tremor of ET is with posture but also may persist during movement and also can be present at rest.[5,6] The tremor frequency of ET is usually faster than that of iPD[7]; however, older patients with ET may have a slower tremor in the range of that typically seen with iPD.[8] Physicians look for other symptoms such as bradykinesia, hypophonia, micrographia, or postural abnormalities to help differentiate between iPD and ET. Nevertheless, the differential diagnosis is often difficult.

In the course of developing a battery of tests to aid in the early and preclinical detection of iPD, patients with ET underwent the test battery. One of the components of the test battery was a wrist flexion and extension task. Unexpectedly, patients with ET were abnormal in performance similar to patients with iPD and different from normal control (NC) individuals. The results of the wrist task performance are reported.

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METHODS

Patients with iPD were defined as having three of the following four symptoms or signs: (1) resting tremor of 4–6 Hz that attenuated with movement, (2) slowing of movement and/or absence of associative movements, (3) rigidity as measured by increased resistance to passive movement, and (4) flexed posture and/or impaired posture-righting reflexes. Patients were excluded if they met any one of the following criteria: (1) history of exposure within the previous 6 months to drugs that either block dopamine receptors or deplete dopamine stores, (2) history of a lack of response to levodopa therapy, (3) weakness, (4) changes in tendon reflexes and/or pathologic reflexes such as a Babinski sign, (5) ataxia, (6) dementia, (7) impairment of vertical gaze, or (8) marked autonomic nervous system abnormalities such as orthostatic hypotension and urinary bladder dysfunction. While these criteria do not exclude the possibility of including patients

with disorders other than iPD, they do lessen the possibility.

ET was defined as the presence of postural tremor in the arms that worsens with action in the absence of any other condition or drug known to cause enhanced physiological tremor and in the absence of cerebellar symptoms or signs.[9] Patients with ET and normal control (NC) subjects were required to meet the same exclusionary criteria as described above for patients with iPD. The diagnosis of iPD or ET was made by movement disorders experts with over 20 years of experience each (E.B.M. and W.C.K.). All subjects and patients gave prior written informed consent and the protocol received prior approval by the institutional review boards (IRB) of the Cleveland Clinic Foundation, the University of Arizona College of Medicine, and The University of Kansas Medical Center.

The motor task consisted of rapid wrist flexion and extension movements made to one of two types of targets known to the subject or patient in response to an auditory "go" signal described previously.[10] Subjects and patients were seated comfortably in front of the instruction panel and manipulandum. The range of motion was divided into seven segments with the end segments 5° wide whereas the interior segments were 12° wide. The instruction panel consisted of two rows of seven light-emitting diodes (LEDs), each corresponding to one of the seven segments of the range of motion. The top row of LEDs represented targets for movement whereas the bottom row represented cursor LEDs indicating present hand position.

Movements to the end segments (1 and 7) were limited by mechanical stops. Movement to these targets constituted the bounded tasks. Thus, subjects and patients did not have to stop the movement carefully. Movement to the interior targets 2 and 6 (adjacent to targets 1 and 7, respectively) required the subjects and patients to stop the movement and constituted the unbounded tasks. Patients and subjects had to hold the wrist in the final target window for 500 msec. Flexion and extension and bounded and unbounded trials were presented in a random order. Wrist position was monitored at 125 samples per second. Reaction times were measured. Movement velocities (degrees per second) were analyzed instead of movement times because the ranges of motion were different between the bounded and unbounded tasks.

Trials began with illumination of an end target LED (target LED 1 for extension or target LED 7 for flexion movements). The subject or patient then moved the hand to align the cursor LED with the target LED. The initial end target LED then extinguished and a target LED at the opposite end illuminated indicating the target for movement. For bounded tasks, either target LED 7 for extension or target LED 1 for flexion movements illuminated. In the case of unbounded tasks, the LED next to the end (target LED 6 for extension or target LED 2 for flexion movements) illuminated. After a random hold time, an auditory "go" signal cued the subject or patient to make a rapid wrist movement to the final target. Patients and subjects had to hold the wrist within the start window for a minimum of 500 msec and within the target window for 500 msec. Failure to hold within these windows resulted in a failed task and the data for that task was discarded. Any patient with tremor amplitude greater than 5° at the wrist would not be able to perform the task and were not included in the study. Thus, patients with ET could have only mild disease.

All patients and subjects used their dominant hand. Subjects and patients were allowed to practice until proficient, as evidenced by reaching a plateau in performance. Data from 10–20 trials of each of the four tasks were collected and analyzed. There were a different number of trials collected for each task because the order of tasks were presented in a pseudorandom order. This means that the tasks were presented in a repeated sequence. Within the sequence, tasks were randomly ordered. This assured that all tasks were performed but in an order that could not be predicted. Repeatedly during data acquisition, subjects and patients were encouraged to react and move as quickly as possible. Subjects and patients were allowed to rest if they became fatigued.

RESULTS

Fifty-six NC subjects were tested with a mean age of 69 years (range, 50–93 yrs; 34 were women). Forty-six patients with iPD were tested who were newly diagnosed. All patients with iPD had bilateral symptoms. The patients with iPD were selected on the basis of mild disease as defined by a Hoehn and Yahr Scale 2. Ten (22%) patients with iPD were not on medication and the 36 (78%) patients with iPD who were taking anti-iPD medications were tested after an overnight fast (at least 8 hrs) from medications. The number of patients with iPD and ET on various combinations of medications are shown in Table 1. Note that the numbers total to more than the number of patients because only two patients were taking only one medication. The mean age of the patients with iPD was 71 years (range, 44–89 yrs; 18 were women). Thirty-four subjects with ET were tested with a mean age of 73 years (range, 53–87 yrs; 12 were women). Twenty-two (65%) patients with ET were not on medication and 12 (35%) were on medications but were tested after an overnight fast (at least 8 hrs) from their medication.

Both patients with iPD with tremor and ET had mild tremor with an amplitude at the wrist of less than 5°. A tremor of any greater amplitude would have exceeded both the start window and the target window for the bounded tasks and the patient would have failed the task. Within subjects and patients the reaction times were not normally distributed (Kolmogrov-Smirnov test) but skewed toward the minimum reaction time. Consequently, median reaction times for each subject or patient for each task were used in subsequent analyses. The distribution of the individual's median reaction times was not normally distributed (Kolmogorov-Smirnov test). Therefore, the reaction times were logarithmically transformed to minimize departure from normalcy.

An analysis of variance (ANOVA) of repeated measures design was performed on the transformed individual's median reaction times (the repeated measure) by group and task. There was a statistically significant group effect ($p < 0.045$) and task effect ($p < 0.008$), but no significant interaction. Paired comparisons used unpaired *t* test (Table 2). A series of planned comparisons were made to test the hypotheses that patients with iPD had prolonged reaction times compared with patients with ET and NC subjects and the reaction times of patients with ET were the same as NC subjects. One-tailed *t* tests were used for those comparisons in which the direction of the expected difference in reaction times were predicted. For other comparisons, a two-tailed *t* test was used. A Bonferroni correction was applied for multiple comparisons with an initial α of 0.10 chosen to maintain power.[11] Thus, there were four tasks in each set of comparisons and a $p \leq 0.025$ was chosen as the level for statistical significance.

Comparisons demonstrated no significant difference in reaction times between patients with ET and NC subjects except in the extension bounded task. Patients with iPD were slower than NC subjects in all tasks except the extension unbounded task. There were no significant differences in reaction times comparing patients with iPD and patients with ET. Results are shown in Table 2.

TABLE 1. *Description of medications taken by patients with idiopathic Parkinson's disease and essential tremor*

	No. of patients with Parkinson's disease
Levodopa	20
Dopamine agonists	6
Anticholinergics	1
Selegiline	23
None	10
	No. of patients with essential tremor
Beta-blockers	8
Primidone	7
Benzodiazepines	4
None	22

Within subjects and patients, the movement velocities were not normally distributed (Kolmogorov-Smirnov test). Consequently, median movement velocities were determined for each subject or patient for each task. The distribution of the median movement velocities for the group of subjects and patients was not normally distributed and therefore were logarithmically transformed. An ANOVA of repeated measures design was performed on the transformed median movement velocities (repeated measure) by group and task. There was a statistically significant group effect ($p < 0.049$) and task effect ($p < 0.001$) but no task-group interaction. A series of planned comparisons were made to test the hypotheses that movement velocities in patients with iPD were slowed compared with patients with ET and were the same in patients with ET as NC subjects. Because the direction of the expected difference in reaction times were known for some comparisons, one-tailed *t* tests were used. For other comparisons, a two-tailed *t* test was used. A Bonferroni correction was applied for multiple comparisons with an α of 0.10 chosen to maintain power. Thus, there were three comparisons for four tasks and a $p \leq 0.008$ was chosen as the level for statistical significance. Results are shown in Table 3. Patients with iPD

TABLE 2. *Median reaction times (25th and 75th percentiles), in milliseconds, for the patients with idiopathic Parkinson's disease (iPD) and essential tremor (ET) and normal control subjects for each task**

Task	iPD median	ET median	NC median	p value ET vs iPD*	p value NC vs ET†	p value iPD vs NC*
Flexion unbounded	405 (353; 450)	380 (325; 430)	360 (270; 440)	NSD	NSD	0.017
Flexion bounded	393 (340; 440)	350 (305; 420)	340 (250; 413)	NSD	NSD	0.008
Extension unbounded	363 (290; 421)	330 (300; 448)	330 (270; 393)	NSD	NSD	NSD
Extension bounded	380 (320; 428)	350 (290; 455)	323 (278; 400)	NSD	0.01	0.016

* Note that the paired comparisons were performed on the logarithmically transformed reaction times but the 25th and 75th percentiles reported are based on the actual reaction times.

NSD, no significant difference with a $p > 0.05$.

For paired comparisons, * indicates a one-tailed unpaired *t* test was used and † indicates a two-tailed test was used.

TABLE 3. *Median (25th and 75th percentiles) of movement velocities in degrees per second for patients with idiopathic Parkinson's disease (iPD) and essential tremor (ET) and normal control subjects for each task**

Task	iPD median	ET median	NC median	p value ET vs iPD*	p value NC vs ET†	p value NC vs iPD*
Flexion unbounded	135 (107–203)	125 (96–171)	144 (123–204)	NSD	0.027?	NSD
Flexion bounded	180 (117–267)	164 (130–206)	200 (168–244)	NSD	0.017	NSD
Extension unbounded	138 (114–191)	144 (104–210)	179 (134–250)	NSD	0.018	0.006
Extension bounded	187 (126–274)	157 (125–208)	216 (175–257)	NSD	0.0013	NSD

* NSD, no significant difference with a $p > 0.05$.
For paired comparisons, * indicates a one-tailed unpaired *t* test was used and † indicates a two-tailed test was used.

were not different from patients with ET. Patients with ET were slower than NC subjects for all tasks. Although there was a tendency for patients with iPD to be slower than NC subjects, the differences reached statistical significance only for the extension-unbounded task. This is consistent with the mild degree of disease in the subjects with iPD.

DISCUSSION

Patients with ET had a tendency toward increased reaction times and statistically significant decreased movement velocities compared with NC subjects and comparable to patients with iPD. To the degree that increased reaction times, in the type of task used in this study, is reflective of akinesia, then patients with ET have akinesia similar to patients with iPD. To the degree that slowed movement velocities in this type of task reflects bradykinesia, then patients with ET had bradykinesia similar to patients with iPD. Akinesia and bradykinesia in patients with ET, in addition to tremor, may further contribute to the difficulty of distinguishing between iPD and ET. However, this can only be stated for early and mild iPD as selected in this project. As the motor dysfunction increases with advanced iPD, there is usually no difficulty distinguishing more advanced iPD from ET.

It is possible that the presence of tremor interfered with motor performance thereby slowing both reaction times and movement velocities. However, the task required holding within windows of 5°. Thus, the patients' tremors had to be less than 5° in amplitude at the wrist. Therefore, tremors were mild in amplitude and unlikely to interfere with motor performance. Further, the bounded tasks did not require high degrees of accuracy in stopping the movement because the movement was limited by mechanical stops. Therefore, at least for the bounded tasks, it is unlikely that concerns for accuracy in the presence of tremor alone resulted in slowing of the movement velocities.

The intriguing question is why should these patients with early iPD and ET, with different underlying pathologies and differences in PET,[12–14] have similar motor dysfunction? Perhaps slowed motor initiation and slowed motor execution are a nonspecific findings and can arise from disease or injury of multiple areas.

One possible explanation, although speculative, is that prolonged reaction times and movement velocities may reflect a system dysfunction, in this case the system is the combination of cerebellar and basal ganglia influences that ultimately reach the motor cortex. In this sense, prolonged reaction times and slowed movement velocities may represent abnormal programming by an intact motor cortex that has been deprived of its normal input from either the basal ganglia or cerebellum. It is possible that early and mild disease, either in the cerebellum or basal ganglia, will have its most pronounced effect at this highest level of integration and specification in the motor cortex. At this level of dysfunction, the symptoms could be referrable to either the basal ganglia in the case of iPD or to the cerebellum in the case of ET. As iPD progresses, the increased and additional abnormalities of motor function come to represent loss of function more specific to the basal ganglia. At this point, the increased symptoms and signs are more easily referable to iPD versus ET. Such a hypothesis could explain why some patients are initially diagnosed as having ET, only later to be diagnosed as iPD.

A system pathophysiology is supported by the numerous examples in which lesions at different locations in the same system produce similar symptomatology. Lesions of the supplementary motor area and globus pallidus produce bradykinesia and akinesia similar to lesions of the substantia nigra pars compacta.[15,16] Similarly, lesions of the frontal, parietal, and occipital lobes, peripheral nervous sensory system, pons, and brachium conjuctivum can produce symptoms indistinguishable from lesions of the cerebellar cortex or deep cerebellar nuclei.[17] Most readers would accept that lesions of the globus pallidus, supplementary motor area, and substantia nigra could produce similar clinical phenomena because these structures lie within the same system. The same would be true for lesions of the cerebellar cortex, cerebellar nuclei, and so on, because these lie within the

same system. The hypothesis offered here only extends this concept by suggesting that the cerebellar and basal ganglia systems do combine into one system that ultimately drives the motor cortex. Different lesions of this common system might be expected to produce similar phenomena.

The concept of a system that combines cerebellar and basal ganglia influences is most evident from studies of tremor in iPD, ET, and other tremors of cerebellar origin. Ablative lesions and chronic high-frequency stimulation of the ventral intermediate nucleus of the thalamus (Vim) reduces tremor from iPD, ET, and other cerebellar disorders. Chronic high-frequency stimulation of Vim effective against iPD tremor is associated with changes in regional blood flow in the cerebellum.[18] A recent case report demonstrated that the tremor of iPD can be altered by the presence of a pre-existing lesion of the cerebellum.[19] Extrapolation of these findings to motor initiation and execution is problematic in that the mechanisms underlying tremor may be different from those underlying motor initiation and execution. However, these observations do provide an example of how the basal ganglia and cerebellum may be linked into a system that, when lesioned, produces tremor.

Generalization from slowed reaction times and movement velocities in a simple reaction time paradigm to the clinical symptoms of akinesia and bradykineisa is problematic. More complex and multisegmented movements reflective of normal movement may be affected differently from simple movements. Nevertheless, the simple reaction time paradigm used here is comparable to tasks that are used in clinical assessments and in the Unified Parkinson Disease Rating Scales. Therefore, the slowing of reaction times and movement times in the simple reaction time paradigm used in this study could complicate assessment of finger tapping and hand opening and closing used in clinical assessment and could cause diagnostic confusion. This would be particularly true early in the course of either ET or iPD. Regardless of the mechanisms underlying slowed reaction times and movement velocities in ET or iPD, these observations should serve as a note of caution in the differential diagnosis of ET from early iPD.

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