Temporal Discrimination Is Altered in Patients With Isolated Asymmetric and Jerky Upper Limb Tremor

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ABSTRACT: Background: Unilateral or very asymmetric upper limb tremors with a jerky appearance are poorly investigated. Their clinical classification is an unsolved problem because their classification as essential tremor versus dystonic tremor is uncertain. To avoid misclassification as essential tremor or premature classification as dystonic tremor, the term indeterminate tremor was suggested.

Objectives: The aim of this study was to characterize this tremor subgroup electrophysiologically and evaluate whether diagnostically meaningful electrophysiological differences exist compared to patients with essential tremor and dystonic tremor.

Methods: We enrolled 29 healthy subjects and 64 patients with tremor: 26 with dystonic tremor, 23 with essential tremor, and 15 patients with upper limb tremor resembling essential tremor but was unusually asymmetric and jerky (indeterminate tremor). We investigated the somatosensory temporal discrimination threshold, the short-interval intracortical inhibition, and the cortical plasticity by paired associative stimulation.

Results: Somatosensory temporal discrimination threshold was significantly increased in patients with dystonic tremor and indeterminate tremor, but it was normal in the essential tremor patients and healthy controls. Significant differences in short-interval intracortical inhibition and paired associative stimulation were not found among the three patient groups and controls.

Conclusion: These results indicate that indeterminate tremor, as defined in this study, shares electrophysiological similarities with dystonic tremor rather than essential tremor. Therefore, we propose that indeterminate tremor should be considered as a separate clinical entity from essential tremor and that it might be dystonic in nature. Somatosensory temporal discrimination appears to be a useful tool in tremor classification. © 2019 International Parkinson and Movement Disorder Society

Key Words: essential; tremor; dystonic tremor; paired associative stimulation; temporal discrimination; tremor

The clinical concept of essential tremor (ET), tremor associated with dystonia, and other monosymptomatic tremor disorders changed considerably over the past few years, and, accordingly, the long-standing consensus criteria of the International and Parkinson Movement Disorder Society (MDS) on tremor1 were recently updated.2 ET is now defined as an isolated tremor syndrome of bilateral upper limb action tremor with a duration of at least 3 years, with or without tremor in other locations and in the absence of other neurological signs. Furthermore, the new consensus introduced the
definition of ET plus, which refers to ET with additional neurological signs of uncertain significance such as impaired tandem gait, memory impairment, and questionable dystonic posturing.

An action tremor resembling ET and rarely a rest tremor may be observed in patients suffering from dystonia.3,4 Tremor in dystonia is labeled as “dystonic tremor” (DT) when it is present in a body part affected by dystonia, whereas the term “tremor associated with dystonia” is used when tremor and dystonia are found in different body parts.2 Some patients with action tremor resembling ET exhibit upper limb tremor that is unilateral or very asymmetric or that is very jerky or irregular, in the absence of overt dystonia or other neurological abnormalities. Little is known about this type of tremor, which, in our experience, is commonly observed in daily practice and remains a diagnostic challenge. In the past, these patients were mostly labeled as unilateral or asymmetric ET, whereas some researchers considered them to be dystonic.5-9 To avoid misclassification as ET or premature classification as DT, the term indeterminate tremor (IT) was suggested.5 However, since then, no studies have been performed to systematically investigate the relationship of IT to ET and DT.

Several electrophysiological techniques have contributed to a better understanding of the pathophysiology of dystonia, demonstrating abnormalities in neuronal plasticity, loss of inhibition, and sensory dysfunction.10 The latter has been widely studied in dystonia by testing the somatosensory temporal discrimination threshold (STDT), a perceptual measure defined as the shortest time interval in which subjects can perceive two stimuli as being separated.11 Patients with dystonia and DT have increased STDT.11-19 The paired-associative stimulation (PAS) paradigm, a well-established noninvasive technique to assess cortical spike-timing–dependent plasticity, has shown exaggerated plasticity in the primary motor cortex in various forms of dystonia.20-23 In contrast, the response to PAS in ET patients is similar to healthy controls.24 However, effects of PAS are highly variable, and the initially reported significant effect in dystonia has not been uniformly replicated.25 Short intracortical inhibition (SICI) is a paired-pulse transcranial magnetic stimulation (TMS) paradigm that is widely used to study inhibitory intracortical neural circuits in the primary motor cortex. It can be elicited by subthreshold conditioning stimulation followed by suprathreshold test stimulation at interstimulus intervals typically ranging between 1 and 5 ms.26 Several studies have demonstrated loss of short intracortical inhibition in various forms of dystonia, and loss of central inhibition has become an electrophysiological hallmark of dystonia.27-30

In the present study, PAS, SICI, and STDT were performed in healthy controls and in groups of patients with ET, DT, and long-standing isolated upper limb tremor with marked asymmetry and/or marked jerkiness, which we called IT. The aim of this article is to characterize the IT electrophysiologically and investigate whether diagnostically meaningful neurophysiological differences exist among patients with ET, DT, and IT.

Participants and Methods

Study Participants and Clinical Assessment

A total of 93 participants were recruited from the outpatient clinics of the National Hospital of Neurology and Neurosurgery in London and the Department of Neurology in Kiel. Informed consent was obtained from all subjects, and the study was approved by the local ethics committee in accord with the Declaration of Helsinki on the use of human subjects in experiments. The 93 participants were subdivided into four age-matched groups: (1) 26 patients with overt segmental primary dystonia. All had a combination of cervical and/or limb dystonia associated with dystonic tremor. Twenty-four patients had dystonic head tremor, of which 4 had dystonic tremor and 20 tremor associated with dystonia in the upper limbs. Two patients had isolated dystonic tremor of the upper limbs without associated head tremor. (2) Twenty-three patients had ET diagnosed according to the current MDS criteria.3 (3) Fifteen patients had IT defined as an upper limb tremor with asymmetry of at least 1 point on the Essential Tremor Rating Assessment Scale (TETRAS)11 and with unusual jerkiness, but without other neurological signs, such as dystonia and parkinsonism. Seven IT patients had an upper limb tremor with mild asymmetry (<1 point on TETRAS), but with definite jerkiness. Seven IT patients had an asymmetry >1 point on TETRAS, 3 had definite jerkiness, and 4 had only slight jerkiness. One IT patient had a unilateral upper limb tremor with definite jerkiness. (4) Twenty-nine healthy controls (HCs) had no history of neurological diseases or family history of tremor or dystonia. All patients had tremor duration of at least 5 years, and task- and position-specific tremors were excluded.

During a face-to-face interview, information regarding clinical and demographic characteristics were collected, and a detailed neurological examination was performed by a clinician with experience in movement disorders. Patients with clinical evidence of somatosensory abnormalities and parkinsonism were excluded from the study. In 4 IT and 2 ET patients with a questionable rest tremor, upper limb tremor was too severe to certainly exclude parkinsonism. Those patients received a DAT scan, which was normal in all cases. Two dystonia patients had a clear dystonic rest tremor. Both patients had a long-standing tremor syndrome for at least 15 years without any evidence of bradykinesia or other parkinsonian signs. Dystonia severity was determined with the Unified Dystonia Rating Scale (UDRS), and tremor was rated with both the Fahn-Tolosa-Marin (FTM) tremor rating scale and the Bain and Findley sphyrography scores.32-34 All patients were videotaped according to a standardized video
protocol. Signed informed consent for videos was obtained from all patients in this study. Four movement disorder specialists (G.D., R.E., J.B., and B.B.) performed a blinded video rating and allocated the tremor patients to one of the three patient groups. Patients who were not unanimously allocated to one group by all four raters were discussed in detail by a telephone conference, and a consensus was achieved in all patients. A Mini-Mental State Examination (MMSE) was performed in order to ensure adequate cognitive function. Patients with a score <26 points were excluded. Further exclusion criteria were other neurological signs; concurrent or recent exposure to drugs potentially causing tremor; presence of known causes of enhanced physiological tremor; and clinical evidence of functional origin of tremor and depression. The majority of patients in this study received oral medications or botulinum neurotoxin injections. All drugs acting on the central nervous system level were withdrawn 1 week before our assessment. Exclusion points were included. Further exclusion criteria were adequate cognitive function. Patients with a score <26 on the Mini-Mental State Examination (MMSE) were excluded. All participants were assessed with standardized protocols by a single neurologist with experience in clinical neurophysiology (F.G.). Each patient was tested in a single experimental session with a duration of approximately 120 minutes. First, the STDT protocol was performed, followed by a TMS protocol including PAS and SICI.

Electrophysiological Assessment

All participants were assessed with standardized protocols by a single neurologist with experience in clinical neurophysiology (F.G.). Each patient was tested in a single experimental session with a duration of approximately 120 minutes. First, the STDT protocol was performed, followed by a TMS protocol including PAS and SICI.

Tactile STDT Stimuli Procedure

STDT was investigated following a procedure reported in several previous studies.\textsuperscript{14,18,19,35-38} The paired tactile stimuli consisted of square-wave electrical pulses delivered by a constant current stimulator (Digitimer DS7-A; Digitimer Ltd, Welwyn Garden City, UK) through surface skin electrodes on the pad of the index finger and on the zygomatic bone bilaterally. STDT of the hands was assessed with the forearms supinated and resting on the patient’s lap. The anode was distally located from the cathode with an interspace of 1.5 cm. Each participant received a series of stimuli with increasing intensity (starting from 1 mA onward) to determine the perceptual threshold. The latter was defined as the minimal intensity at which a subject perceived the electric stimuli in 10 of 10 trials. STDT was then tested by delivering pairs of stimuli, starting with an interstimulus interval of 0 ms and progressively increasing the interval in steps of 10 ms. The interstimulus interval at which subjects recognized the two separate tactile stimuli in three consecutive trials was defined as the STDT. For each hand and each cheek, paired stimuli were delivered in three separate blocks, and the three values were averaged and used for the data analysis.

Paired Associative Stimulation and Short-Interval Intracortical Inhibition

For the TMS protocol, participants were seated in a comfortable reclining chair, and electromyographic recordings were performed from the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles with Ag-AgCl surface electrodes. In every patient, recordings were performed from the less tremulous hand. For TMS, a standard 70-mm figure-of-eight coil connected to a Magstim 200 BiStim\textsuperscript{2} stimulator (Magstim Co Ltd, Whitland, UK) was used. The stimulating coil was positioned tangentially to the head with the handle pointing backward and laterally at an angle of approximately 45 degrees to obtain motor-evoked potentials (MEPs) in the APB muscle. To obtain the “hot spot” for the APB muscle, the coil was systematically changed in position until the largest MEP was obtained. Stimulation intensity for the test MEP was chosen to produce a MEP of approximately 1-mV amplitude in the APB muscle. Subsequently, the active motor threshold of the APB muscle was determined according to the standard definitions.\textsuperscript{39} SICI was used to probe primary motor cortex intracortical inhibition before and after PAS. SICI was assessed with paired-pulse paradigm, as previously reported.\textsuperscript{26,38} The intensity of the conditioning stimulus was set at 70\%, 80\%, or 90\% of the active motor threshold using an interstimulus interval of 2.5 msec. For SICI, 20 MEPs were collected for each conditioning stimulus and 20 MEPs for the test stimulus alone. Accordingly, each TMS block consisted of 80 MEPs that were randomly applied. Recordings were performed before (baseline) PAS and 0 (T0), 15 (T15), and 30 minutes (T30) after PAS.

PAS consisted of 200 electrical stimuli applied on the median nerve at the wrist through bipolar electrodes (200-μs duration, intensity set at 300\% of the perceptual threshold). Each electrical pulse was followed, after 25 ms, by a TMS pulse over the APB hot spot.\textsuperscript{24} The paired stimulation rate was 0.25 Hz, and the intensity of the test TMS pulse was adjusted to produce 1-mV MEPs (peak-to-peak amplitude) in the resting APB.

Statistical Analysis

The Kruskal-Wallis test was used to compare the four groups for baseline clinical characteristics (age, tremor duration, FTM tremor scores, Bain and Findley spiral scores, and MMSE scores). Pearson’s chi-square test was applied to test for group differences regarding categorical variables (sex, handedness, family history, and tremor characteristics). Electrophysiological data were tested for normality using the Shapiro-Wilk test, and because data were normally distributed, parametric tests were applied. Separate mixed-model analyses of variance (ANOVAs) were performed to test STDT, SICI, and PAS data. The ANOVA for STDT had one between-subject factor:
“group” (four levels: ET, DT, IT, and HC) and two within-subject factors: “stimulus side” (two levels: right, left) and “stimulus location” (two levels: index finger, zygomatic bone). ANOVA for evaluating the conditioning effect of PAS on mean MEP amplitude and SICI had one between-subject factor: “group” (four levels: ET, DT, IT, and HC) and two within-subject factors: “time” (three levels: T0, T15, and T30), “muscle” (APB, FDI), and SICI additionally had an additional subject factor “stimulus intensity” (three levels: 70%, 80%, and 90% of the active motor threshold). Mauchly’s sphericity test was performed, and Greenhouse-Geisser correction was applied when needed. Levene’s test was used to check homogeneity of variance (all nonsignificant). Effects were considered significant if $P < 0.05$. Bonferroni correction was applied for post-hoc analysis. Additionally, a one-way between-groups multivariate analysis of variance (MANOVA) was performed, with group being the independent variable and STDT, SICI, and PAS measures being the dependent variables.

Spearman rank correlation was used to test for possible correlations between demographic features (disease duration, age of onset, and severity of tremor) and electrophysiology measures.

A receiver operating characteristic analysis was used to assess the ability of STDT testing to differentiate each patient group from HCs.

## Results

### Clinical and Demographic Data

Group clinical and demographic characteristics of subjects with ET, DT, and IT are summarized in Table 1 (see also Supporting Information).

### STDT

The ANOVA demonstrated no significant main effect of “side” ($F_{1,85} = 0.022; P = 0.882$) or “group × side” interaction ($F_{3,85} = 0.314; P = 0.815$). However, there was a significant main effect of “location” ($F_{1,85} = 15.430; P < 0.01$; partial $\eta^2 = 0.154$). There was no “group × location” ($F_{3,85} = 1.936; P = 0.13$) or “side × location” interaction.

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**TABLE 1. Biographical and clinical data**

| Patient no. | HC | ET | IT | DT | $P$ Value |
|-------------|----|----|----|----|-----------|
| Sex (M/F)   | 17/12 | 17/6 | 4/11 | 8/18 | 0.001 |
| Age (yr)    | 59.5 ± 12.1 | 60.6 ± 15.1 | 64.9 ± 12.1 | 58.0 ± 14.7 | 0.350 |
| Tremor duration (yr) | — | 32.5 ± 16.9 | 33.2 ± 16.9 | 27.2 ± 15.3 | 0.348 |
| Family history of tremor | — | 18 (78%) | 12 (80%) | 13 (69%) | 0.050 |
| Alcohol response | — | 10 (43%) | 5 (33%) | 12 (46%) | 0.838 |
| Handedness (R/L) | 28/1 | 21/2 | 14/1 | 24/2 | 0.468 |
| MMSE | 28.9 ± 1.0 | 28.7 ± 0.8 | 28.7 ± 1.2 | 28.7 ± 1.2 | 0.809 |
| FTMRS | — | 30.5 ± 11.9 | 37.9 ± 17.9 | 36.4 ± 18.9 | 0.347 |
| UDRS | — | — | — | 5.4 ± 3.1 | 0.603 |
| Bain Scores dominant | — | 4.0 ± 1.4 | 4.4 ± 2.1 | 3.7 ± 2.0 | 0.294 |
| Bain Scores nondominant | — | 4.8 ± 1.7 | 6.0 ± 2.5 | 4.8 ± 2.5 | 0.294 |

All means are expressed ± standard deviation.
M, male; F, female; R, right; L, left; FTMRS, Fahn-Tolosa-Marin rating scale.

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**FIG. 1.** Somatosensory temporal discrimination threshold (STDT) in healthy controls (HC) and in patients with essential tremor (ET), indeterminate tremor (IT) and dystonic tremor (DT). Somatosensory temporal discrimination threshold was tested at the right and left index finger (A) and the right and left zygomatic bone (B). Bars represent mean value with standard errors. Abbreviations: ms = milliseconds.
Because of the significant main effect of “group” (F_{3,85} = 6.553; P < 0.01; partial \( \eta^2 = 0.188 \)), post-hoc analysis revealed that STDT values in patients were significantly higher than in HCs. Accordingly, only the location of stimulation and the patient group allocation demonstrated significant differences. Because of the significant location difference, we analyzed STDT values from face and finger separately.

The STDT values for the hands of each patient group are illustrated in Figure 1A. Mixed-model ANOVA revealed a significant main effect of “group” regarding the STDT values of the finger (F_{3,86} = 16.296; P < 0.001; partial \( \eta^2 = 0.362 \)). Post-hoc analysis demonstrated that STDT values measured in the finger were significantly increased in patients with ET compared to HCs and patients with DT compared to ET patients and HCs (HC vs. DT, P < 0.0001; HC vs. IT, P < 0.0001; ET vs. IT, P = 0.019; ET vs. DT, P < 0.0001). In contrast, patients with ET had STDT values comparable to HCs (P = 0.828).

Figure 1B depicts the mean STDT values determined in the face. Mixed-model ANOVA performed on STDT face data revealed a significant group effect (F_{3,57} = 8.995; P < 0.0001; partial \( \eta^2 = 0.239 \)). Post-hoc testing revealed that STDT values measured on the face were significantly increased in patients with DT compared to HC and ET. There was no difference between IT and ET, but there was a significant difference between IT and HC (HC vs. DT, P < 0.0001; HC vs. IT, P = 0.029; ET vs. IT, P = 0.153; ET vs. DT, P = 0.002).

Stimulation intensity used for STDT testing was not significantly different between groups or locations (each \( P > 0.05 \)). Spearman rank correlation disclosed no significant correlation between STDT abnormalities and disease duration, age of onset, and severity of tremor in the tested patient groups.

The receiver operating characteristic curve analysis for the STDT values of the finger demonstrated 100% sensitivity and 79.3% specificity for a cut-off value of 105 ms in discriminating patients with DT against HCs, whereas a cut-off value of 122 ms had 76.9% sensitivity and 71.4% specificity for discriminating DT against ET. For separating IT from HC, a cut-off value of 105 ms had 86.7% sensitivity and 79.3% specificity, whereas a cut-off value of 122 ms had 60% sensitivity and 71.4% specificity in discriminating IT from ET.

**PAS and SICI**

Data demonstrating the effect of PAS on mean MEP amplitudes are shown in Figure 2. The ANOVA of the PAS data revealed no significant interaction among factors “time” (F_{1,91} = 124.473; P = 0.06), “muscle” (F_{1,65} = 0.408; P = 0.52), and “group” (F_{3,65} = 1.391; P = 0.25).

Figures 3 and 4 illustrate the SICI recruitment curve in the four subject groups, determined at either the APB or the FDI muscle before and after the PAS intervention. Mixed-model ANOVA revealed that SICI produced a decrease in mean conditioned MEP amplitude demonstrated by a strong effect of “stimulus intensity” (F_{2,58} = 58.461; P < 0.001). However, there was no main effect of factors “muscle” (F_{1,59} = 1.529; P = 0.221) and “time” (F_{3,57} = 0.266; P = 0.85), and there were no significance differences among the four subject groups (F_{3,59} = 0.742; P = 0.532).

![Image](image_url)
The MANOVA revealed a significant effect of the patient groups on the combined dependent variables ($F_{30,159.2} = 2.14; P = 0.001$; Wilk’s lambda = 0.370; partial $\eta^2 = 0.28$). When the results for the dependent variables were considered separately, the only difference to reach statistical significance after Bonferroni correction was significantly increased STDT values in IT and DT compared to ET and HC (HC vs. DT, $P < 0.0001$; HC vs. IT, $P < 0.0001$; ET vs. IT, $P < 0.01$; ET vs. DT, $P < 0.0001$).

**Discussion**

The main finding of the present study is that STDT was altered in patients with an isolated asymmetric and jerky upper limb tremor, defined here as IT, and in patients with DT, whereas it was normal in patients with ET. PAS and SICI did not differ statistically among the three tremor groups and HCs, despite a trend toward a smaller SICI and a larger effect of PAS in DT and IT. Based on these results, we propose that IT shares pathophysiological similarities with DT, and that STDT might be a useful tool to discriminate IT from ET.

In addition to abnormal plasticity and loss of inhibition, sensory abnormalities are believed to be an electrophysiologically distinctive feature of dystonia. So far, only two reports with relatively small sample sizes did not find STDT abnormalities in patients with dystonia.\(^40,41\) Our STDT results are in line with a larger number of studies demonstrating normal STDT values in ET and increased STDT values in dystonia and DT compared to HCs.\(^11-19,38,42,43\) In particular, a recent work with a large sample size of different forms of tremor found that an STDT value of 120 ms could discriminate DT from ET, consistent with our finding of abnormal STDT values in patients with IT and DT, but not in ET.\(^43\) This result was most pronounced in STDT data from the index finger, compared to the face. One group found that STDT abnormalities among patients with ET, isolated head tremor, and isolated voice tremor did not differ among testing locations.\(^18\) This discrepancy might be attributable to the fact that, despite our care to avoid it, the stimulating electrodes on the face were close to facial muscles; thus, a slight twitch might have helped patients with DT and IT in their task. Indeed, STDT values from the face were lower.
than STDT values obtained from finger stimulation in DT and IT.

Abnormal STDT was reported in the context of movement disorders other than dystonia, namely Parkinson’s disease (PD) and MSA. To exclude patients with underlying parkinsonian tremor, all patients with rest tremor suspicious for PD received an ioflupane I123 dopamine transporter scan (DAT scan), and tremor duration of at least 5 years in the absence of clinical signs of parkinsonism was required for all patients. None of the four blinded raters detected any overt dystonia in the IT group, and none of the patients had a family history of dystonia.

Similar abnormal STDT values were reported in patients with isolated head and voice tremors. The underlying pathophysiology of these focal tremors is still unclear, and the new consensus statement on the classification of tremors excludes focal tremors from ET and ET plus and classifies them as a unique subgroup. Nevertheless, it is well known that focal tremors can precede clinically obvious dystonia for many years, and isolated head tremor is generally suggestive of concomitant dystonia. Furthermore, voice tremor can be observed in genetically proven dystonia carriers, such as ANO3 and DYT6, without clinical dystonia.

Patients with markedly asymmetric and jerky limb tremor remain controversial in clinical diagnosis, particularly when PD is excluded and no definite dystonia is present. Clinically significant jerkiness and symmetry are not operationally defined for the axis I classification of tremors. Accordingly, the limits of jerkiness and asymmetry compatible with ET and indicative of DT are still undetermined. Our results clearly demonstrate the importance of clarifying these issues in future quantitative studies.

Meanwhile, we have shown that IT patients, like DT patients, have abnormal STDT values, whereas STDT is normal in ET. In addition to this electrophysiological similarity between IT and DT, there were similarities in tremor distribution, regularity, and symmetry (see Supporting Information Table S1). Head and voice tremors were common clinical features in IT and DT, but only a minority of ET patients exhibited tremor in the head or voice. Additionally, the vast majority of patients with DT had asymmetric or jerky upper limb tremor. This is in line with a previous study demonstrating that most patients with DT present with an asymmetric or even unilateral postural or kinetic tremor with a jerky appearance similar to our patients with IT. It is genetically proven that dystonia can present with tremor as the only initial clinical sign, and our data suggest that very asymmetric or jerky upper limb tremor is likely to be a harbinger or variant of DT, not ET. Although we demonstrate clear clinical

FIG. 4. Short latency intracortical inhibition (SICI) recorded from the first dorsal interosseous muscle obtained with stimulus intensities of 70, 80, and 90% of active motor threshold in healthy controls (HC) and in patients with essential tremor (ET), indeterminate tremor (IT) and dystonic tremor (DT) before (A) and 0 (B), 15 (C) and 30 (D) minutes after paired associative stimulation. The amount of inhibition is displayed as the size of the conditioned motor-evoked potential (MEP) as a percentage of MEP evoked by the test pulse alone. Error bars represent standard error of the mean.
and electrophysiological similarities between DT and IT, it is possible that ≥1 IT patients had an unusual phenotype of PD. However, we think this is very unlikely given the fact that none of the IT patients had clinical signs of parkinsonism, despite a mean tremor duration of over 30 years, and all IT patients with rest tremor had a negative DAT scan.

Several studies recently demonstrated enhanced plasticity of sensorimotor circuits using PAS in patients with different forms of dystonia. However, several recent works could not replicate these findings, and the effect of PAS seems to be highly variable. The results of our study support these observations of high variability in all four groups. Although a clear trend is noted, with a more pronounced facilitation after PAS in the DT and IT groups, statistical significance was not reached. Furthermore, we could not demonstrate a clear spread of the effect to nontarget muscles as reported before. In the past few years, it has become obvious that many external and internal variables influence the magnitude of PAS response in both HC and patients suffering from dystonia. In the present study, we tried to reduce these factors by following a strict standardized electrophysiological protocol in homogenous groups. Nevertheless, even a very accurate experimental design is unlikely to control all potential variables and intersubject variability in PAS. Thus, enhanced response to PAS should not be considered a dystonic fingerprint.

Besides enhanced plasticity, loss of inhibition is considered to be a characteristic electrophysiological feature of dystonia. Reduced SICI was demonstrated in patients with dystonia in several previous studies, suggesting an abnormality of intracortical inhibitory neurons, whereas paired-pulse TMS studies revealed normal cortical excitability in ET patients. Baseline comparisons of SICI among the four groups in our study revealed no statistical differences. Additionally, we could not demonstrate any changes in SICI following the administration of PAS in the three patient groups. These observations are in line with several reports of SICI being within the normal range in dystonic patients. This might be explained, to some degree, by the fact that SICI and PAS exhibit large intra- and interindividual variability. Furthermore, it is possible that the sample size is too small to identify statistical differences in these techniques.

The identification of patients with very jerky tremor was purely subjective in this study and based on the experience of four examiners. Asymmetry, by contrast, was rigorously defined using the metric anchors of TETRAS. It is possible that a more quantitative definition of jerkiness using motion transducers would be valuable in classifying patients with IT versus ET. A larger threshold for asymmetry in upper limb tremor might also be useful. A one-point difference in tremor amplitude means that the tremor in one limb is approximately twice as large as the other.

In conclusion, we demonstrate that patients with isolated jerky and asymmetric upper limb tremor share clinical and electrophysiological similarities with DT rather than with ET. Based on our data, we suggest that IT, as defined in this study, might be considered as a separate clinical entity from ET and that IT might be dystonic in nature. STDT appears to be a useful tool in the clinical classification of tremor, and additional studies are needed to quantitatively delineate the kinematic and electrophysiological properties that are useful in tremor classification.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.