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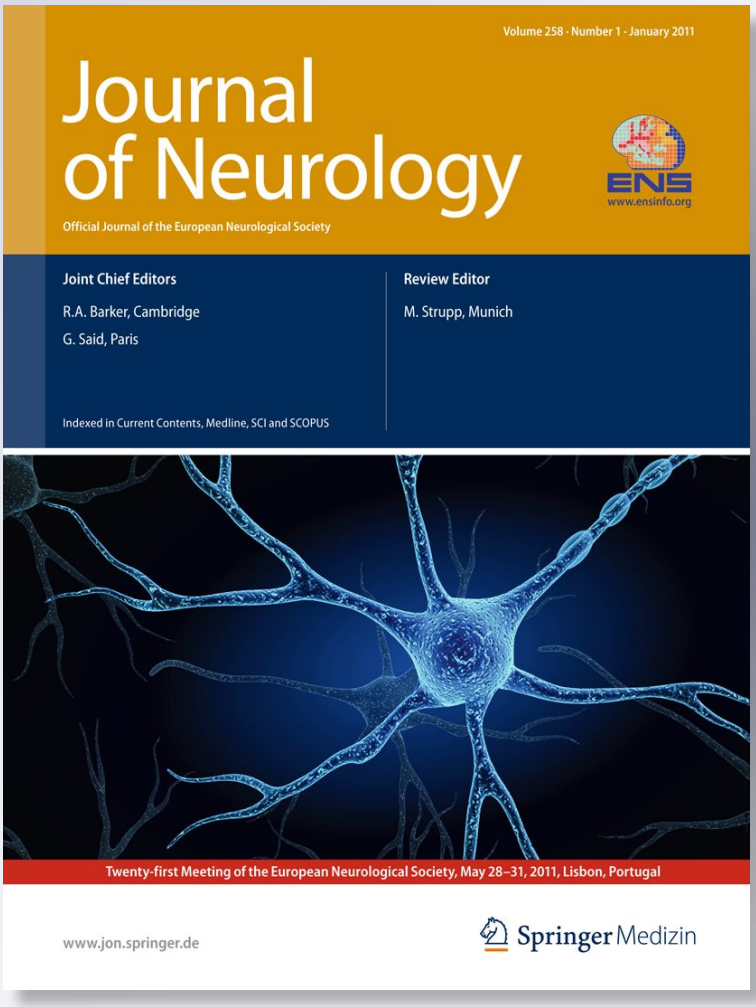

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ORIGINAL COMMUNICATION

Temporal discrimination thresholds in adult-onset primary torsion dystonia: an analysis by task type and by dystonia phenotype

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Abstract Adult-onset primary torsion dystonia (AOPTD) is an autosomal dominant disorder with markedly reduced penetrance. Sensory abnormalities are present in AOPTD and also in unaffected relatives, possibly indicating non-manifesting gene carriage (acting as an endophenotype). The temporal discrimination threshold (TDT) is the shortest time interval at which two stimuli are detected to be asynchronous. We aimed to compare the sensitivity and specificity of three different TDT tasks (visual, tactile and mixed/visual-tactile). We also aimed to examine the sensitivity of TDTs in different AOPTD phenotypes. To examine tasks, we tested TDT in 41 patients and 51 controls using visual (2 lights), tactile (non-painful electrical stimulation) and mixed (1 light, 1 electrical) stimuli. To investigate phenotypes, we examined 71 AOPTD patients (37 cervical dystonia, 14 writer's cramp, 9 blepharospasm, 11 spasmodic dysphonia) and 8 musician's dystonia patients. The upper limit of normal was defined as control mean +2.5 SD. In dystonia patients, the visual task detected abnormalities in 35/41 (85%), the tactile task in 35/41 (85%) and the mixed task in 26/41 (63%); the mixed task was less sensitive than the other two ($p = 0.04$). Specificity was 100% for the visual and tactile tasks. Abnormal TDTs were found in 36 of 37 (97.3%) cervical dystonia, 12 of 14 (85.7%) writer's cramp, 8 of 9 (88.8%) blepharospasm, 10 of 11 (90.1%) spasmodic dysphonia patients and 5 of 8 (62.5%) musicians. The visual and tactile tasks were found to be more sensitive than the mixed task. Temporal discrimination threshold results were comparable across common adult-onset primary torsion dystonia phenotypes, with lower sensitivity in the musicians.

Keywords Dystonia · Temporal discrimination threshold (TDT) · Genetics · Endophenotype

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Background

Adult-onset primary torsion dystonia (AOPTD) is a common movement disorder associated with significant morbidity; the pathophysiology is incompletely understood. Epidemiological studies suggest that although most cases appear to be sporadic, the disorder is autosomal dominant with penetrance of 12–15% [1–3]. Despite recent important developments such as the identification of DYT6 (a mutation in THAP1 associated with some adult-onset laryngeal phenotypes) [4], progress in identifying the genetics of AOPTD has been slow.

The endophenotype approach to genetic studies in poorly penetrant disorders was first described over 30 years ago, and a number candidate endophenotypes have been investigated in AOPTD [5–12]. The temporal discrimination threshold (TDT) is defined as the shortest time interval at which two stimuli can be determined to be asynchronous and is a promising AOPTD endophenotype [13]. This sensory testing modality may be used to demonstrate

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abnormal temporal processing in AOPTD patients and relatives [14], and is probably a marker of basal ganglia (putaminal) dysfunction [14, 15] and possibly of dopaminergic pathway dysfunction in particular [16].

In this paper, we aimed to assess the sensitivity and specificity of three different modalities of TDT testing (visual, tactile and mixed stimuli) and to examine the ability of TDT to detect basal ganglia dysfunction (sensitivity) in a variety of AOPTD phenotypes. We hypothesized that the multimodal mixed task would be less sensitive than the other two based on a trend demonstrated in a previous study [14] and that TDT testing would be equally sensitive across phenotypes.

Patients and methods

AOPTD patients

For the assessment of the task type in TDT testing, three tasks (visual, tactile and mixed) were examined in 41 patients (mean age 52, range 21–73 years; 25 cervical dystonia, 4 musician's dystonia, one spasmodic dysphonia and 11 writer's cramp patients). Following the results of this initial analysis, the mixed task was omitted from the study, and the visual and tactile tasks only were used for additional subjects.

For the determination of the prevalence of abnormal TDT in different AOPTD phenotypes therefore, TDT was analysed using two modalities (visual and tactile). We tested an additional 38 patients, and the results for the original 41 patients were adjusted to include only their visual and tactile results. Thus, a total of 79 patients were examined for phenotype analysis comprising 71 AOPTD patients [37 cervical dystonia (mean age 56.4 years), 14 writer's cramp (mean age 53.3 years), 9 blepharospasm (mean age 63.9 years), 11 spasmodic dysphonia (mean age 48.0 years)] in addition to 8 musician's dystonia patients (mean age 45.8 years). The results of the visual and tactile TDTs were averaged to give an overall measure of the subjects' temporal discrimination ability.

The diagnosis of dystonia and characterisation of phenotype were carried out in a dedicated dystonia clinic by two neurologists with expertise in movement disorders. A subset of these patients ($n = 29$) has been reported in previous studies from our group [13, 14].

Control participants

Fifty-one healthy control subjects were recruited from hospital staff and visitors to the hospital. Exclusion criteria were a history of neurological disease including neuropathy, visual disorder or a history of cerebral, cervical or brachial plexus injury, and a family history of dystonia. Control subjects were divided into two groups: under 50 years of age ($n = 34$; mean age 31 years; range 22–49) and over 50 years of age ($n = 17$; mean age 58 years, range 50–71). This resulted in two control groups, within which there was no correlation between age and TDT result, allowing standardised Z scores to be calculated as described below. All controls performed all three tasks, and their results (either for all three tasks or the visual + tactile tasks only) were used in analyses as appropriate.

Sensory testing

TDT testing was carried out as described previously [14]. Briefly, testing was carried out in a single session in a sound-proof air-conditioned room. For the comparison of TDT task type, subjects were tested for three modalities: a visual task (two flashing LED lights), a tactile task (non-painful electrical stimulation of the index and middle finger) and a mixed task (one LED light and electrical stimulation of one finger). Stimuli were presented at 5-s intervals, and the separation between pairs of stimuli was increased in 5-ms steps. The LEDs were positioned 7° into the subject's peripheral field on the side being tested. LEDs were illuminated for 5 ms each presentation. Electrical stimuli were presented using square-wave stimulators (Lafayette Instruments Europe, LE12 7XT, UK) and rectangular cloth electrodes (item no. TD-141C1, Discount Disposables, P.O. Box 111, St. Albans, VT, 05478). Stimulus pulse length was set at 5 ms, and stimulus current was increased (in 0.1 mA steps) until the subject could reliably detect the stimuli. Each task was performed four times on each side of the body with the median of the four trials in each condition (side × task) taken to eliminate practice effect. For the comparison of phenotypes, two modalities were tested (visual and tactile) using the same experimental protocol. This resulted in a total of 6 conditions/24 trials for the three-task TDT session or 4 conditions/16 trials where only visual and tactile tasks were carried out. The results of the conditions were then averaged to determine the overall TDT in milliseconds.

Statistical analysis

All TDT results (in milliseconds) were converted to standardised Z scores to enable easy comparison of individual results using the formula;

$$Z\ \text{Score} = \frac{\text{Actual TDT} - \text{Age-related control mean TDT}}{\text{Age-related control standard deviation}}$$

The control mean and standard deviation used in the formula depend on the age of the subject being calculated

(over or under 50 years) and whether the two-task or three-task TDT is being used; the relevant figures are shown in Table 1 and in the Results section. Z scores of equal to or greater than 2.5 were considered abnormal.

Analysis of the frequency of abnormal results between two groups was carried out using Fischer's exact test ($p < 0.05$ considered statistically significant, corrected for multiple comparisons where relevant). Linear regression was used to correlate visual and tactile TDT results and generate an r^2 value in an effort to demonstrate that single-modality TDT testing measures temporal discrimination consistently irrespective of method of measurement. Paired t test was used to compare side of body in musicians for each task type separately.

Results

Control participants

Control subjects were divided into two groups: under 50 years ($n = 34$) and over 50 years ($n = 17$). The mean TDT in the under 50 group was 24.3 ms (SD 8.9 ms) for the three-task model (visual, tactile and mixed) and 23.7 ms (SD 8.3 ms) for the two-task model (visual and tactile only). The mean TDT in the over 50 group was 30.9 ms (SD 5.5 ms) for the three-task model and 29.7 ms (SD 5.9 ms) for the two-task model. Control results for the individual tasks are presented in Table 1. None of the control Z scores using either the three-task or two-task model fell above the cutoff of Z score = 2.5; thus, there were no false-positive TDT results. Of note, however, one control subject had a mixed TDT result just above the normal cutoff ($Z = 2.58$); this individual had visual and tactile results within normal limits.

Comparison of tasks

Abnormal visual TDTs were found in 35/41 (85%) AOPTD patients, abnormal tactile TDTs in 35/41 (85%) and abnormal mixed TDTs in 26/41 (63%) (Fig. 1). There was a significant difference between the reduced frequency of abnormal TDTs using the mixed task compared to either of the other two modalities (Fisher's exact test $p = 0.041$). The pattern of reduced rates of abnormal TDT tests in the mixed task held when subjects were divided into younger and older age groups (under 50 years: visual 79%, tactile 71%, mixed 42%; over 50 years: visual 89%, tactile 92%, mixed 74%), although patient numbers in these subgroups were insufficient to allow testing for statistical significance (power calculation for the difference seen in the overall group is $n = 60$, with $\alpha = 0.05$, power = 0.8). In the 51 control subjects, the mean mixed TDT was greater than either the mean visual or tactile TDT (25.7 ms for mixed compared to 23.5 and 23.8 ms for visual and tactile respectively under 50 years; 33.2 ms for mixed compared to 30.2 and 29.3 ms for visual and tactile respectively over 50 years). In addition, the standard deviation was greater for the mixed task under 50 years (Table 1). There was relatively good correlation between raw results for visual

Table 1 The raw temporal discrimination threshold (TDT) results with standard deviations (ms) along with mean and range of Z scores in the two control groups, the four adult-onset primary torsion dystonia (AOPTD) groups (combined and separate) and the musicians. The results reported in the AOPTD patients and musicians are the two-task (visual and tactile) combined TDT results

	N	Mean TDT (ms)	SD (ms)	Mean Z score	Range Z score
Control < 50 (3 tasks)	34	24.3	8.9	0	−1.7 to 1.8
Control < 50 (2 tasks)	34	23.7	8.3	0	−1.5 to 2.0
Control < 50 visual task	34	23.5	8.6	0.0	−1.6 to 2.1
Control < 50 tactile task	34	23.8	8.9	0.0	−1.8 to 2.1
Control < 50 mixed task	34	25.7	11.8	0.0	−1.7 to 2.6
Control > 50 (3 tasks)	17	30.9	5.5	0.0	−2.2 to 1.4
Control > 50 (2 tasks)	17	29.7	5.9	0.0	−2.0 to 1.2
Control > 50 visual task	17	30.2	6.8	0.0	−1.7 to 1.6
Control > 50 tactile task	17	29.3	6.4	0.0	−2.0 to 2.0
Control > 50 mixed task	17	33.2	6.7	0.0	−2.0 to 1.8
AOPTD (2-task)	71	72.5	24.8	6.9	−0.9 to 19.5
Cervical dystonia (2-task)	37	67.6	18.7	6.6	−0.8 to 13.9
Writer's cramp (2-task)	14	71.2	30.7	6.9	−0.9 to 14.6
Blepharospasm (2-task)	9	84.8	37.8	9.2	2.3 to 19.5
Spasmodic dysphonia (2-task)	11	83.2	24.1	8.2	1.1 to 12.7
Musician's dystonia (2-task)	8	55.1	19.8	4.2	0.8 to 7.5

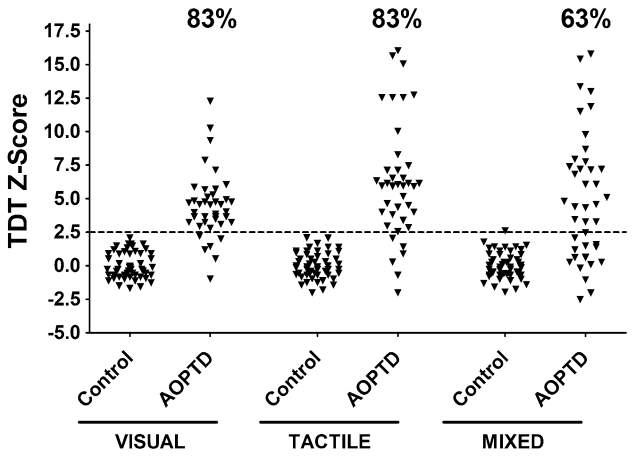

Fig. 1 Temporal discrimination threshold (TDT) *Z* scores for three TDT modalities (visual, tactile and mixed) in 51 healthy control subjects and 41 adult-onset primary torsion dystonia (AOPTD) patients. The rates of abnormal TDTs were similar (85%) using the visual and tactile tasks; the mixed task was less sensitive at 63% ($p = 0.041$)

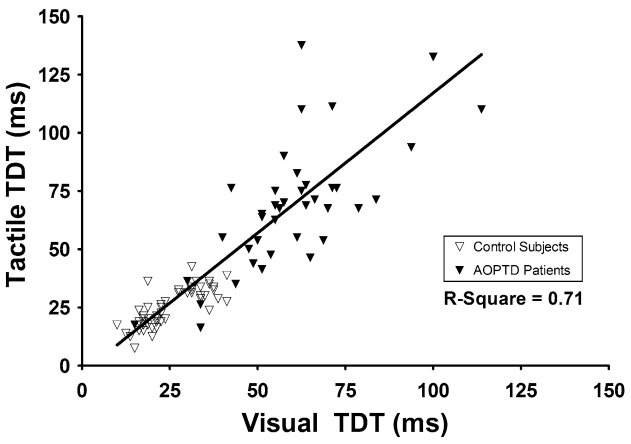

Fig. 2 Scatter plot of raw visual versus tactile temporal discrimination thresholds (TDTs) (ms) in 51 healthy control subjects (*open symbols*) and 41 adult-onset primary torsion dystonia (AOPTD) patients (*filled symbols*) demonstrating the correlation between the two tasks

and tactile TDT testing when examined across the 51 control subjects and 41 AOPTD patients with an r^2 of 0.71 (Fig. 2).

Comparison of phenotypes

Abnormal TDTs (using the two-task visual and tactile model) were found in 36/37 (97.3%) cervical dystonia (CD) patients, 12/14 (85.7%) writer's cramp (WC) patients, 8 of 9 (88.8%) blepharospasm (BEB) patients, 10 of 11 (90.1%) spasmodic dysphonia (SD) patients and 5 of 8 (62.5%) with musician's dystonia (Fig. 3). The numerical results for the patient groups are presented in Table 1. There was no statistically significant difference between the first four phenotypes tested (CD, BEB, SD, WC), but the frequency of abnormal TDTs was significantly lower in musician's dystonia patients when compared to these other phenotypes grouped together (Fisher's exact test $p = 0.03$). Comparing each side of the body in the musicians, there was no statistical difference in TDT results for the visual (paired *t* test $p > 0.05$) and more importantly the tactile (paired *t* test $p > 0.05$) task. Interestingly, a further analysis that grouped the writer's cramp patients and musicians together as "focal hand dystonia" and compared them to the other three groups combined "other dystonia" (cervical dystonia, spasmodic dysphonia, blepharospasm) generated a statistically significant difference in the proportion of abnormal results (17/22 for "focal hand" vs. 54/57 for "other dystonia"; Fischer's exact test = 0.034). However, writer's cramp alone compared to "other dystonia" generated a non-significant result (12/14 for "writer's cramp" vs. 54/57 for "other dystonia"; Fischer's exact test = 0.254), suggesting that the former result is driven by the musicians in this study and suggesting that the writer's cramp patients behave like the other AOPTD phenotypes in terms of TDT abnormalities. Five AOPTD patients had a normal two-task TDT (Table 2). There were no consistent characteristics to suggest a subgroup that had a lower TDT sensitivity.

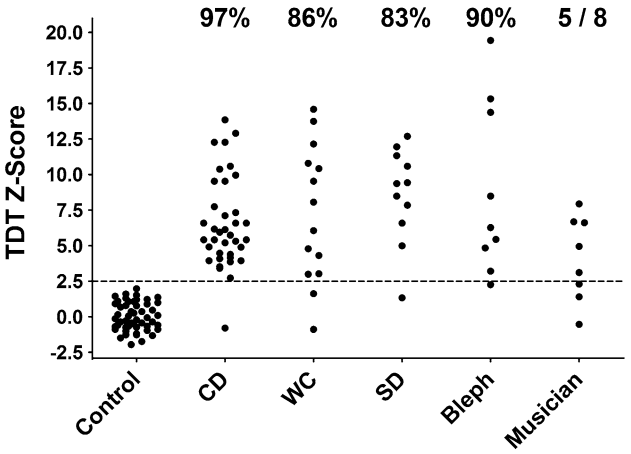

Fig. 3 Temporal discrimination threshold (TDT) *Z* scores in 51 healthy control subjects and in the adult-onset primary torsion dystonia (AOPTD) phenotypes: abnormal TDTs were found in 36 of 37 (97.3%) cervical dystonia (CD) patients, 12 of 14 (85.7%) writer's cramp (WC) patients, 8 of 9 (88.8%) blepharospasm (Bleph) patients, 10 of 11 (90.1%) spasmodic dysphonia (SD) patients and 5 of 8 (62.5%) of musicians tested

Discussion

We have found that the mixed visual-tactile task is significantly less sensitive than pure visual or tactile tasks in

Table 2 The characteristics of the five adult-onset primary torsion dystonia (AOPTD) patients (excluding musicians) that had normal temporal discrimination threshold (TDT) results

Z score	Phenotype	Family history	Age
−0.8	Cervical dystonia	Familial	60
1.62	Writer's cramp	Sporadic	60
1.33	Spasmodic dysphonia	Familial	27
2.24	Blepharospasm	Sporadic	70
−0.89	Writer's cramp	Familial	40

detecting abnormal temporal discrimination in a cohort of AOPTD patients with various phenotypes. In studying DYT1 patients, Fiorio et al. [11] also found that the mixed task was less useful with greater spread of control results. It is likely that the cross-modal nature of the task was responsible for the differences in the sensitivity of the mixed task versus the uni-modal tasks. In contrast to the uni-modal tasks, additional processing is involved when stimuli from different modalities are presented. This processing may involve additional brain regions, specific to cross-modal processing [17], and therefore may introduce variability into the TDT. The standard deviation of the mixed TDT task was greater than that of the uni-modal tasks, and thus the upper range of normal was increased. This has implications for the practical application of TDT in recruiting AOPTD patients and unaffected relatives for genetic studies. The visual and tactile modalities had equal sensitivity; thus, when simple uni-modal stimuli are used, abnormal temporal processing by the basal ganglia is reliably detected.

The finding of similar frequencies of abnormalities in cervical dystonia, writer's cramp, spasmodic dysphonia and blepharospasm patients suggests that putaminal dysfunction, reflected by the abnormal TDT, is a fundamental and state-independent disorder not related to phenotype or disease characteristics. We have previously reported data suggesting that subclinical putaminal enlargement is present in both AOPTD patients and unaffected relatives with abnormal TDTs [14], which supports the hypothesis that TDT is measuring a marker of AOPTD gene carriage. Furthermore, Scontrini et al. [18] found abnormal TDT results, at the group level, in various AOPTD phenotypes compared to control subjects and that the body region tested did not significantly affect the finding of abnormal TDT.

TDT testing using pure visual or tactile stimuli is therefore a sensitive measure, capable of objectively identifying marked temporal processing deficits in individual AOPTD patients reflecting basal ganglia dysfunction. We propose that TDT will be of use as an endophenotype in studies of patients with all forms of AOPTD and their unaffected relatives. The five AOPTD patients (excluding musicians) who had normal TDT results are detailed in Table 2; there was no consistent feature in phenotype, age or family history to suggest a subgroup in whom TDT is less useful, and at the group level no statistical differences were seen between phenotypes.

TDT may therefore prove most fruitful in identifying non-manifesting gene carriers in AOPTD families for inclusion in linkage analyses, transmission disequilibrium testing studies or exome sequencing techniques. However, it is also possible that the technique may have other applications, including the differentiation of basal ganglia disorders from drug-induced or non-organic movement disorders.

The results in the small musician's dystonia group differ from the other patients in this study. It has been suggested that musician's dystonia may be multifactorial; in addition to the prevailing hypothesis of central motor and sensory dysfunction induced by repetitive and highly practiced motor activity [19–23], there may be a genetic predisposition [24]. The lower prevalence of abnormal TDTs in musician's dystonia compared to focal hand dystonia suggests either clinical or diagnostic heterogeneity; some patients may represent focal task-specific dystonia and others a secondary movement disorder. It might be considered that the tactile TDT performance in musicians would be superior to other subjects, but there is no evidence to support this in our data (Table 1). Furthermore, as abnormal TDT results do not appear to be lateralised in focal dystonia [11, 12, 14] and indeed there is no statistical difference in TDT results from either side for both visual and tactile in the musicians in our study, one cannot attribute our findings to superior performance in the unaffected limb.

Conclusion

TDT testing using uni-modal stimuli is a sensitive marker of putaminal dysfunction in AOPTD; multimodal techniques seem to be less reliable. TDT testing is equally sensitive across all tested AOPTD phenotypes and should therefore be a useful tool in performing genetic studies in families with all common forms of AOPTD. The small cohort of musician's dystonia patients in this paper behaves differently and may be heterogeneous in aetiology; further

study is warranted. TDT likely represents a reliable and sensitive endophenotype in on-going efforts to identify AOPTD-related genes.

Ethical approval: Ethical approval for this work was granted by the Ethics and Medical Research Committee, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

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Conflict of interest The authors have no disclosures or conflict of interest.

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