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Measurement & Analysis of the Temporal Discrimination Threshold

Applied to Cervical Dystonia

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**SHORT ABSTRACT:**

Methods for the measurement and analysis of the temporal discrimination threshold and its application in the study of the pathogenesis cervical dystonia.

**LONG ABSTRACT:**

The temporal discrimination threshold (TDT) is the shortest time interval at which an observer can discriminate two sequential stimuli as being asynchronous (typically 30–50ms). It has been shown to be abnormal (prolonged) in neurological disorders, including cervical dystonia, a phenotype of adult onset idiopathic isolated focal dystonia. The TDT is a quantitative measure of the ability to perceive rapid changes in the environment and considered indicative of the behavior of the visual neurons in the superior colliculus, a key node in covert attentional orienting. This article sets out methods for measuring the TDT (including two hardware options and two modes of stimuli presentation). We also explore two approaches of data analysis and TDT calculation. The application of the assessment of temporal discrimination to the understanding of the pathogenesis of cervical dystonia and adult onset idiopathic isolated focal dystonia is also discussed.

**INTRODUCTION:**

Temporal discrimination describes a person’s ability to discriminate, or perceive, rapid changes in their environment. The temporal discrimination threshold (TDT) is the shortest time interval at which an individual can perceive that two sequential sensory stimuli are asynchronous. Temporal discrimination has been shown to be abnormally prolonged in disorders affecting the basal ganglia, including dystonia1-7.

Dystonia is the third most common neurological movement disorder – after Parkinson’s disease and Essential Tremor. It is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements or postures8. Dystonia can affect any part of the body. When it affects one body part it is known as focal dystonia8. Dystonia affecting the neck muscles is known as cervical dystonia, the most common phenotype of adult onset idiopathic isolated focal dystonia.9,10 The pathogenesis of cervical dystonia remains unknown; it is considered to be a genetic disorder with autosomal dominant inheritance with markedly reduced penetrance. Environmental factors are important in relation to disease penetrance and expression.

The superior colliculus, a sensorimotor structure situated in the dorsal midbrain, is important for the rapid detection of environmental stimuli in the process of covert attentional orienting 2,13,14. Visual stimuli access the superior colliculus rapidly through the retino-tectal magnocellular pathway. The TDT is a simple, objective measure of the processing of visual (and other sensory stimuli) in the superficial layers of the superior colliculus. The TDT has been studied in individuals with cervical dystonia, their unaffected relatives and healthy control participants. Compared to age and sex matched control participants, an abnormal TDT has high sensitivity (97%) and specificity (98-100%) in cervical dystonia1. An abnormal TDT is found in 50% of unaffected first-degree female relatives of patients with cervical dystonia, demonstrating age- and sex-related penetrance with autosomal dominant inheritance11,12. An abnormal TDT in unaffected relatives of cervical dystonia patients (compared to relatives with normal TDTs) is associated with increased putaminal volume (by voxel-based morphometry) and reduced putaminal activity (by fMRI). The superior colliculus is considered a significant node in the neuronal network which is dysfunctional in cervical dystonia14 and the assessment of temporal discrimination provide important clues as to the pathomechanisms underlying cervical dystonia.

The goal of this article is to present two methods for measuring and analyzing temporal discrimination, as well as demonstrating the application of this method to studying the pathophysiology of cervical dystonia.

**PROTOCOL:**

1. **Hardware Solutions**

The visual stimuli need to be presented in a consistent manner with precise inter-stimulus interval. Two hardware options have been developed for this purpose.

* 1. TDT hardware - Table-Top Method
* The table-top method was created by the Trinity Centre for Bioengineering, Trinity College Dublin, employing a microprocessor to control the illumination of two yellow light-emitting diodes (LED’s), with 5 mm diameter, Figure 1.
* The LEDs, encased in a box, are placed on the table in front of the participant and positioned 7° from the subject’s centre point on the side being tested.
* The box is oriented such that the LEDs are vertically aligned.
* This experiment is conducted in a sound-proof, darkened room.
* The LEDs have a luminance of 90cd/m2. A small amount of background luminance was required to enable the operator to see enough to run the experiment.

[Place Figure 1 here]

1.2) TDT Hardware – Portable TDT Headset

* The second hardware solution is a portable headset, also designed in-house at the Trinity Centre for Bioengineering, Trinity College Dublin, and previously described5,15.
* The headset was developed from laser-sintered nylon plastic called ‘Strong & Flexible’ and weighs 0.70 kg.
* 3D printing files for this headset are available to download from www.dystoniaresesarch.ie/X;
* The device is strong, flexible and has a low transparency index.
* The colour black was chosen to minimize light penetrance.
* The visual stimuli are provided by a pair of vertically oriented yellow LEDs, with a 5 mm diameter, positioned at the rear of the right and left arms of the headset.
* A small red LED (3 mm diameter), serves as a fixation point. This fixation point is also positioned at the rear of the left and right arms of the headset. It is located mid-way between the yellow LEDs, but situated on the opposite side of the end panel, such that it is closer to the centre of the device, Figure 1.
* Mirrors, positioned in the centre part of the device, in front of the user’s eyes, reflect the LEDs from the back of the device such that they appear 70 to the left or right side of the subject’s centre.
* The focal distance is 350 mm. This was found to be sufficient to ensure focus, regardless the participant’s age.
* A rubber sealant surrounds the eyepiece. This both provides comfort for the participant and negates the effect of ambient lighting conditions. As such, this devices is suitable for use at any location.
* The fixed form of the device provides consistency in distance and angles between stimuli and participant.
* The headset is driven by a compact control unit centred on a microcontroller (Arduino Nano3) connected to the device.
* The luminance of the LEDs is 90 cd/m2.

1. **Instructions to Participants**

* For both the table-top and headset methods, participants are asked to focus on the fixation point in the midline and not to look directly at the flashing LEDs.
* The participant is instructed to respond “same” or “different” following presentation of each stimulus pair, depending on whether they perceive the stimuli to be synchronous or asynchronous. Sample responses are provided in Table 1(a).

1. **Section: Stimulus Presentation**

Two approaches to stimulus presentation have been employed.

* 1. Staircase method
* Stimuli are presented every 5s with the inter-stimulus interval starting at 0 and becoming progressively more asynchronous (increasing from by 5ms) each time.
* The trial ends when a participant responds “different” for three consecutive pairs of stimuli.
* The first of these asynchronous responses is taken as the temporal threshold for that trial.
* There are four presentation modalities: (i) left top LED first, (ii) left bottom LED first, (iii) right top LED first, and (iv) right bottom LED first.
* The procedure is run twice for each modality, resulting in a total of eight runs.
  1. Random Presentation Method
* Similar to the staircase method, stimuli pairs are presented every 5s. However, in this instance the inter-stimulus interval varies, in a randomized fashion, from 0-100ms.
* The same four presentation modalities are employed here, and repeated, giving a total of eight runs, as with the staircase method.
* The duration of a trial of randomized presentation is dictated by the protocol as opposed to the subject’s responses, and lasts a total of 2 minutes.

1. **Data Analysis**
   1. Single TDT value

* Using the data from the staircase method, calculate the temporal discrimination threshold for each participant by taking the median of the thresholds from each of the eight runs.
* This gives a single TDT value (in milliseconds) per individual.
* The Z-score is defined as the difference between the participant’s TDT, and the mean TDT from an age-matched control population, divided by the standard deviation of the TDT values for that control population.
* A Zscore >2.5 is deemed to reflect an abnormal TDT.
  1. Distribution Analysis
* Encode the response data such that ‘0’ corresponds to “same” and ‘1’ corresponds to “different”, Table 1(a).
* In the case of staircase presentation only, pad out the data to ensure all runs are the same length as the longest run. This is done by assuming all subsequent responses, following termination of a run, are “different”. An illustrative example is provided in Table 1(b). Note, it is not necessary to pad the data following random presentation, as all runs are, by default, of equal length.
* Average participant responses across trials and plot as a function of stimulus asynchrony.
* Fit the data with a cumulative Gaussian function.
* The mean of this distribution represents the point at which participants are equally likely to respond ‘same’ or ‘different’. This point is referred to as the ‘point of subjective equality’ (PSE). The standard deviation of the Gaussian distribution, also referred to as the ‘just noticeable difference’ (JND), indicates how sensitive participants are to changes in temporal asynchrony around their mean.
* Estimate the 95% confidence intervals for the TDT and the PSE and JND of the psychometric function.
* The MATLAB.exe to perform the above distribution analysis can be downloaded from [www.XXXX](http://www.XXXX), see Butler et. al for full description of this method15.

Data from the random presentation approach can be analyzed to determine the single or distributed TDT, as described above. However, due to the random presentation order of inter-stimuli intervals, these data must first be ordered (from smallest to largest inter-stimulus interval), prior to subjecting it to the analysis described above for data arising from the staircase presentation method.

**REPRESENTATIVE RESULTS:**

* 1. Single TDT value

Examples of filled score sheets are provided in Tables 1 & 2, where these respectively represent results following staircase and random stimulus presentation methods. The thresholds for each run (the timing of the first of three stimulus pairs deemed to be ‘different’), are highlighted. Note that the results from the random stimulus presentation method, Table 2, must be ordered prior to processing, such that the inter-stimulus interval increases sequentially (as is the case by default with the staircase method). Once the alignment is correct, the TDT and Z-score can be calculated. In the case of Table 1, the TDT is calculated as 25 ms (i.e. the median of 40, 25, 25, 25, 45, 25, 40, 10). These data are taken from a 35 year old women who participated in a previous study16. The mean and standard deviation for TDT values from women in this age bracket, was XXX. Therefore the Z-score for this individual participate is:

* 1. Distribution Analysis

Key stages in the distribution analysis are illustrated in Tables 1 (data padding & response averaging) and Figure 2. The sample data used in this analysis is from the same subject as that discussed above and shown in Tables 1 & 2. The plots in Figure 2 are generated from the downloadable MATLAB.exe file. The left side shows the observed data, the cumulative Gaussian fit (following 2000 iterations), and the bootstrapped fits. The goodness of fit measure is illustrated on the right hand side. Also shown are the temporal discrimination thresholds, the fit parameters, the point of subjective equality (PSE), and just noticeable difference (JND) values. The right side shows goodness of fit measure the loglikelihood ratio (Deviance) for the observed data (red horizontal line) and the Monte-Carlo generated loglikelihood ratio distribution and the 95% confidence intervals (dashed horizontal lines).

The same MATLAB executable exports the TDT, PSE and JND values and bootstrapped cut-offs of 2.5%, 25%, 50%, 75% and 97.5% confidence intervals as well as the goodness of fit Deviance and cutoffs to an excel file. Table 3 provides the outputs generated for the data in Tables 1 and 2. By way of comparison, the TDT values obtained by direct analysis, and calculation of the median of each of the 8 thresholds, from the staircase and random stimulus presentation, are 25ms and 50ms respectively; whereas Table 3 provides the TDT values obtained following bootstrapping of the data. These are 23.75 and 48.75ms respectively.

**FIGURES & TABLES:**

**Figure 1:** (a) Schematic of the design of the headset. A pair of yellow LEDs and the red fixation LED, are placed on the left and right side of the participant via a head mounted unit and made visible by way of reflection in the mirrors in front of the user. (b) Schematic blown-up 3D model of the headset. Taken from Butler (2015). (c) The LED stimulus unit for table-top presentation.

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| **Table 1**: Sample data following staircase presentation method, with interstimulus intervals (ISI) increasing by 5ms each time. (a) Data shown for each of the two conditions (top LED first x2, and bottom LED first x2) for the right and left hand sides, giving a total of eight runs. 's' means 'same', 'd' means 'different'. The calculation of TDT is shown. Please note the time intervals used to calculate the TDT are the ISI's corresponding to the first of three consecutive 'different' responses. B. The same data as shown in (a), but it has been encoded such that a '0' represents a response of 'same', and '1' represents 'different'. Data padding (to the longest run) is illustrated. This is a pre-processing step prior to applying the distribution analysis. (c) Averaged responses for each ISI, note these values are used in the distribution see Figure 2.  **Table 2:** Responses from the same participant as Table 1, this time stimuli are presented with randomised interstimulus intervals (ISI). (a) Data for the two conditions (top LED first x2, and bottom LED first x2) on the right hand side. For compactness, the data from the left hand side are not shown here. However, all eight runs are used in all analysis. (b) The same data sorted by incrementing ISI |
|

**Table 3**: Summary of Gaussian distribution and goodness of fit analysis for the results from the staircase presentation method shown in Table 1, and random presentation method shown in Table 2 (right side only)

**Figure 2:** and Goodness of Fit Analysis. The left hand column shows Gaussian Distribution for (a) results following the staircase method of stimulus presentation, and (b) the random method of stimulus presentation. The black dots show the proportion of perceived ‘different’ responses as a function of inter-stimulus interval, or temporal asynchrony. The light grey curves represent the 2000 Gaussian functions that were fitted to the bootstrapped data. The dark grey curve represents the average cumulative Gaussian function. Values for the Point of Subjective Equality (PSE) (mean) and Just Noticeable Difference (JND) (standard deviation) are also given above each graph. In addition, the TDT value, calculated from the full distribution is shown.

**DISCUSSION:**

***TDT Measurement & Analysis***

This article presents two forms of apparatus (table-top and headset), two methods of stimulus presentation, and two approaches to data analysis to quantify a person’s temporal discrimination ability. Protocol options are also discussed. The portable headset provides a convenient hardware option that ensures consistency in distance and angles between the participant and the LED light sources while also allowing data to be collected in any convenient location. Molloy et al. compared the traditional table-top and the headset solutions for stimulus delivery and found the headset to be reliable and accurate5.

Two methods of stimulus presentation are described; a staircase and a randomised approach. The ‘staircase’ approach is the most common method of stimulus presentation for visual and tactile temporal discrimination protocols6,7,12,17,18. This technique, which presents non-randomised progressively asynchronous stimuli, may be considered to contribute to a potential learning effect. This possibility was specifically tested by McGovern and colleagues16; the ‘staircase’ method was shown to be a robust approach with consistent results across repeated experiments16. This study also revealed that the randomised stimuli presentation method yields consistently longer TDT values compared with the existing staircase method (mean TDTRANDOM = 55.08 ms; mean TDTSTAIRCASE = 30.57 ms for 30 healthy controls). While both presentation methods are valid, the difference in resulting TDT values emphasizes the importance of maintaining uniformity in experimental technique selection within and across studies from a given laboratory. In addition care should be taken when comparing absolute TDT values across studies (from patients and controls).

Finally we presented two methods of data analysis. The first, standard analysis method, results in a single threshold value for each of the eight runs; where that threshold is the inter-stimulus interval of the first of three stimulus pairs identified as being asynchronous. The median of the eight thresholds is taken as that person’s TDT value. In order to overcome the potential limitations of having a single value, a second, more sophisticated, approach has also been presented. Using this analysis a participant’s data is fitted with a cumulative Gaussian distribution and the mean and standard deviation extracted. In addition, the data are submitted to a non-parametric bootstrapped analysis to get 95% confidence intervals for each participant’s data15. This method of data analysis offers the potential to gain deeper insight into differences in visual perception, particularly when examining differences within and between control and patient groups.

***Application of TDT to understanding the pathophysiology of Cervical Dystonia***

An abnormal TDT can be interpreted as an impaired ability to detect or discriminate environmental change. The superior colliculus, in the dorsal midbrain, plays a critical role in detecting and reacting to salient stimuli21. Although a complex structure, it can be functionally separated into two layers21. The visuosensory neurons in the superficial layer receive direct input from the visual system. Whereas the premotor and cephalomotor neurons in the deep layer project have multiple projections, including control of the muscles of the eyes, neck and head. Superior collicular activity is modulated by gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter22. Inhibitory GABAergic activity limits the duration of the transient burst response in both the visuosensory neurons in the superficial layer and the premotor neurons in the deep layer of the superior colliculus23. In response to a visual stimulus, the visual neurons in the superficial layer exhibit a transient ‘ON’ response. GABAergic inhibition then silences this response, enabling the neurons to be ready to respond again when they detect a change in the environment as the visual stimulus is turned off. If there is insufficient GABA, these neurons may become dysfunctionally active23. It is hypothesised that insufficient GABAergic inhibition results in prolonged duration firing of the visual neurons, giving rise to abnormal temporal discrimination, and prolonged TDT values. In addition, the abnormal movements characteristic of cervical dystonia, are hypothesised to *also* result from insufficient GABAergic inhibition, this time of the cephalomotor neurons in the deep layers of the superior colliculus.

Cervical dystonia is the most common phenotype of adult onset focal dystonia9,10; its pathogenesis remains unknown. Over twenty monogenic inherited dystonias and dystonia-related disorders have been reported, and causal genes identified19. However, the majority of adult onset isolated dystonias have unknown genetic causation. An endophenotype is a subclinical marker of genetic carriage which can help us understand disease pathomechanisms. The TDT is proposed as a potential endophenotype for adult onset focal dystonia2,4 and has been found to be abnormal in up to 97% of patients and approximately 50% of their clinically unaffected relatives1,3,4. Temporal discrimination is affected by age20. In addition, abnormal TDT has been shown to follow an age- and sex-related pattern similar to that of cervical dystonia12. These findings suggest autosomal dominant inheritance and support the use of the TDT as an endophenotype for adult onset focal dystonia, and in particular, cervical dystonia.

This manuscript and accompanying video have provided a guide on how to measure and analyse a participant’s visual temporal discrimination. In addition, the application of TDT to the study of cervical dystonia has been outlined (with the aid of animated graphics in the video), both in the context of a reliable endophenotype, and as a potential tool to shed light on the pathomechanisms of this disorder.

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