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Non-parametric bootstrapping method for measuring the temporal discrimination threshold for movement disorders

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Abstract

Objective. Recent studies have proposed that the temporal discrimination threshold (TDT), the shortest detectable time period between two stimuli, is a possible endophenotype for adult onset idiopathic isolated focal dystonia (AOIFD). Patients with AOIFD, the third most common movement disorder, and their first-degree relatives have been shown to have abnormal visual and tactile TDTs. For this reason it is important to fully characterize each participant's data. To date the TDT has only been reported as a single value. **Approach.** Here, we fit individual participant data with a cumulative Gaussian to extract the mean and standard deviation of the distribution. The mean represents the point of subjective equality (PSE), the inter-stimulus interval at which participants are equally likely to respond that two stimuli are one stimulus (synchronous) or two different stimuli (asynchronous). The standard deviation represents the just noticeable difference (JND) which is how sensitive participants are to changes in temporal asynchrony around the PSE. We extended this method by submitting the data to a non-parametric bootstrapped analysis to get 95% confidence intervals on individual participant data. **Main results.** Both the JND and PSE correlate with the TDT value but are independent of each other. Hence this suggests that they represent different facets of the TDT. Furthermore, we divided groups by age and compared the TDT, PSE, and JND values. The analysis revealed a statistical difference for the PSE which was only trending for the TDT. **Significance.** The analysis method will enable deeper analysis of the TDT to leverage subtle differences within and between control and patient groups, not apparent in the standard TDT measure.

 Online supplementary data available from stacks.iop.org/JNE/12/046026/mmedia

Keywords: temporal discrimination, neurological measurement, movement disorders, non-parametric bootstrapping

1. Introduction

Adult-onset idiopathic isolated focal dystonia (AOIFD) is the most common form of dystonia; most patients appear to have sporadic AOIFD but up to 25% have another affected

family member (Stojanovic *et al* 1995, Leube *et al* 1997). Familial AOIFD is inherited in an autosomal dominant fashion with a penetrance as low as 12–15% (Waddy *et al* 1991). The use of a sensitive endophenotype, a marker of subclinical gene carriage in unaffected relatives, is one

approach to studying this problem (Hutchinson *et al* 2013, Kimmich *et al* 2014).

The temporal discrimination threshold (TDT) is the shortest time interval at which a participant can detect that two stimuli, here two LEDs in peripheral vision, are asynchronous. The TDT has a number of benefits over other possible AOIFD endophenotype candidates such as the spatial discrimination threshold which has a strong age-dependence (O'Dwyer *et al* 2005, Walsh *et al* 2007). The TDT has been shown to be abnormal in Parkinson's disease (Artieda *et al* 1992, Lee *et al* 2005), writer's cramp (Fiorio *et al* 2003), in DYT1 carriers (Fiorio *et al* 2007), multiple system atrophy (Lyoo *et al* 2007), blepharospasm (Fiorio *et al* 2008), patients with cervical dystonia (Bradley *et al* 2012), and up to 50% of unaffected first degree female AOIFD relatives over 48 years (Kimmich *et al* 2014). Using fMRI (Pastor *et al* 2004) and (Rao *et al* 2001) showed activation of the basal ganglia for temporal discrimination. This was further examined by (Bradley *et al* 2009) using voxel-based morphometry to investigate difference in the putaminal structure of unaffected relatives of AOIFD patients with and without abnormal TDTs. The results showed that unaffected relatives with an abnormal TDT had larger putaminal structure than the unaffected relatives with a normal TDT. Hence suggesting that a disorder of the basal ganglia would result in an abnormal TDT.

To further strengthen the case for TDT as a clinically applicable endophenotype, data from patients and relatives living at a distance from the laboratory are required. In a recent paper we addressed this concern by designing a highly portable light-weight method for presenting and acquiring participant data in the field (Molloy *et al* 2014).

While the TDT has yielded very important and interesting findings, we believe that the TDT data have not been explored to their full potential. One possible criticism is that it results in only a single value, a threshold expressed in milliseconds, for each participant. Here, we fit the data with a psychometric function which yields a point of subjective equality (PSE) and a just-noticeable difference (JND) value for each participant. Furthermore, we employ a non-parametric bootstrapping method to fit 95% confidence intervals upon the individual participant data.

2. Participants

Seventy-eight healthy control participants were recruited. All participants had normal cognition, normal visual acuity, absence of sensory symptoms and a normal clinical examination by a neurologist. Participants were excluded if they had a history of a neurological disorder such as dystonia, parkinsonism or a family history of dystonia; any condition resulting in loss of visual acuity that might affect ability to perceive the visual stimulus; or any history of cognitive impairment that could affect ability to understand and participate in the experiment.

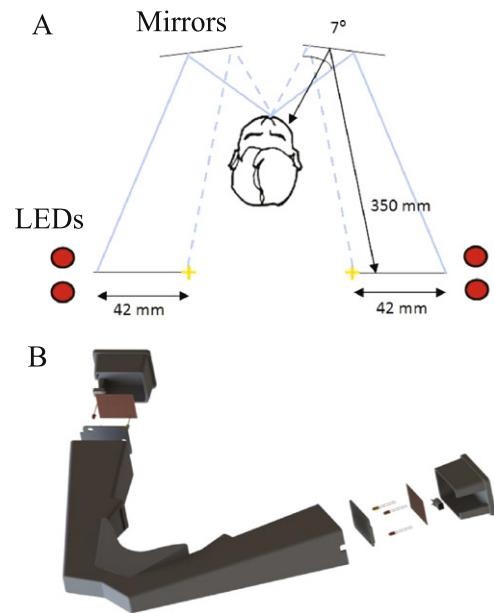


Figure 1. (A) Schematic of the design of the headset. Reflected measurement of visual temporal discrimination threshold, with a pair of LEDs placed on the left and right side of the participant via a head mounted unit. (B) Schematic blown-up 3D model of the headset.

3. Apparatus and methods

3.1. Apparatus

The visual TDT measurement previously have been carried out in a dimly lit room, placing the stimulating lights on a table in front of the participant. Here participants wore a headset with consistent position relative to the stimulus, a more reliable method for stimulus presentation.

A head-mounted unit was designed as a shell in which the stimulating LEDs were placed. It conferred a fixed focal length and ambient luminance for the stimulation setup. This shell was fitted as a headset fixed on the head of the participant with a comfortable stable and adjustable strapping system. Elements of this unit are described below:

3.2. Materials and technology

The head-mounted unit was created using a 3D plotting system. The material used was a sintered nylon plastic called 'Strong and Flexible', which has a high strength and high flexibility with high capabilities of detail design, low transparency index and low glossiness; the colour black was chosen for this application to minimize light penetrance.

For technological reasons, the head-mounted unit was divided into 12 elements that were printed separately; the 3D printer files are included as supplementary materials (available at stacks.iop.org/JNE/12/046026/mmedia). The elements fitted together without glue and the connections between elements do not allow light to penetrate the experimental environment, but permit further prototype adjustments figure 1(B).

3.3. Stimulus delivery

To ensure that the setup is a portable light-weight stand-alone device an Arduino Nano 3.0 with LCD screen for display was employed to input participant information, stimulus presentation and to record and output responses to a computer.

3.4. Temporal discrimination threshold

TDT was measured using pairs of visual stimuli presented to the participant in a single session at different locations, often at a distance from the laboratory. The LEDs were placed 7° into the participant's peripheral vision on the side of the body being tested as in figure 1(A). The stimuli were synchronized initially and were progressively separated in 5 ms steps. When the participant reported that the pairs of stimuli were asynchronous on three consecutive occasions the block was stopped, the first of these is taken as the TDT. The task was performed four times on each side of the body in random order, resulting in a total of eight runs per participant. The order was randomized to minimize practice or attention effect.

3.5. Participant TDT

The TDT for each participant was calculated by taking the median of the four runs for each side; these results were averaged to obtain a TDT value.

3.6. Participant TDT psychometric function fit

To further characterize the data we assessed another method of analyzing the data in which a cumulative Gaussian psychometric function was fitted to the proportion of asynchronous judgments made by participants (figure 2). To do this 0 corresponded to a participant responding 'same' (synchronous), while 1 corresponded to the participant responding 'different' (asynchronous). Due to the design of the experimental protocol the number of asynchronous presentations did not have to be the same for each run, as a run was terminated when a participant responded 'different' three times in a row. For this reason in cases where the number of presentations of trials were not the same for all runs, all responses were assumed 'different' following the termination of the run and the data were padded accordingly such that all the runs were the same length as the longest run. The responses were averaged across trials and plotted as a function of stimulus asynchrony and the data were fitted with a cumulative Gaussian function.

For each participant fit the mean and slope values were extracted; the mean value corresponds to a cumulative probability of 0.5, the PSE. The slope value is proportional to the standard deviation of the Gaussian, which is a measure of sensitivity, the JND. Thus the lower the JND the more sensitive the participant is to the change in temporal discrimination around their PSE.

3.7. Non-parametric bootstrapped method

Each participant's dataset was submitted to a non-parametric bootstrapping procedure to estimate the 95% confidence intervals for the TDT and the PSE and JND of the psychometric function (Efron and Tibshirani 1993). The procedure entailed generating new data sets by sampling with replacement from the original responses within each time step. For each random data set we calculated a TDT and fitted a psychometric function. This was carried out 2000 times to estimate the 95% confidence intervals (light grey lines in figure 2).

3.8. Goodness of fit

The log-likelihood ratio was used to calculate the goodness of fit for each participant known as deviance,

$$D = 2 \sum_{i=1}^K \left(n_i y_i \log \left(\frac{y_i}{p_i} \right) + n_i (1 - y_i) \log \left(\frac{1 - y_i}{1 - p_i} \right) \right),$$

where K is the number of time points, n_i is the number of repetitions at that time point, generally eight repetitions, y_i is the observed proportion of asynchronous responses, p_i is the proportion of asynchronous responses predicted by the fitted curve. A deviance value of 0 means a perfect fit (Wichmann and Hill 2001a).

Monte-Carlo based techniques were used to generate 10 000 data sets from the best-fitting cumulative Gaussian. For each of the generated data sets the Deviance was calculated to paint the deviance distribution, which reflects the deviances expected from an observer whose responses are the best fitting Cumulative Gaussian. From the Deviance distribution 95% confidence intervals are defined, if the observed Deviance (D) is outside of the 95% confidence intervals then the data does not satisfy the goodness of fit criteria.

3.9. Comparison of the classical TDT method and the psychometric method

To investigate the relationship between the parameters three correlation analyses were carried out; (1) the TDT versus the PSE; (2) the TDT versus the JND; (3) the JND versus the PSE. We report the beta and standard error values of the fit with corresponding t -values and p values and the r values with the corresponding F -values and p values.

3.10. Group level analysis

To investigate the effect of age on the TDT, the 78 participants were divided into two groups; under 35 years of age ($n=41$; mean age 28.13, range 20–35) and over 35 years; ($n=37$; mean age 46.23; range 36–65). The TDT, PSE, and JND values from each group were submitted to unpaired t -tests for comparison. To correct for multiple comparisons we set the alpha level to 0.0167.

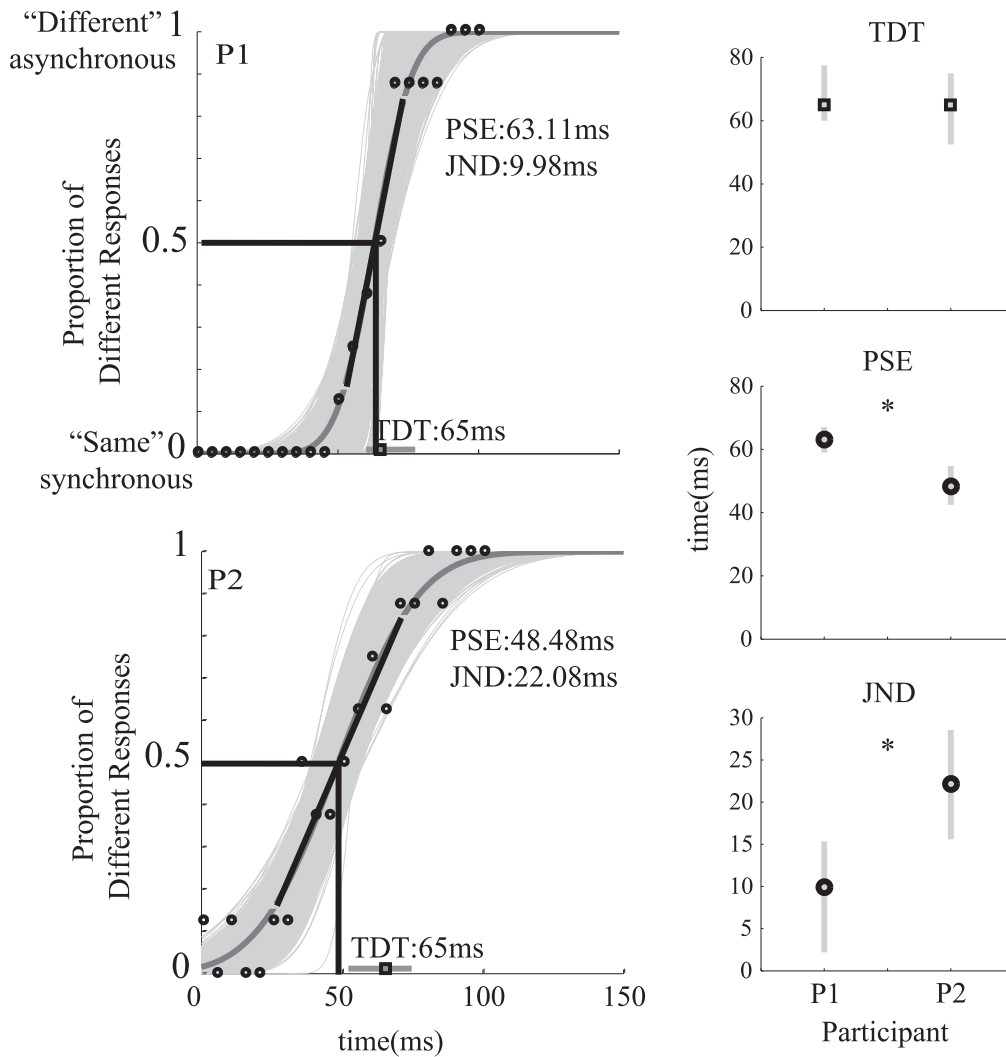


Figure 2. Data from two participants. Left side: the black dots show the proportion of perceived ‘different’ responses as a function of temporal asynchrony. The light grey curves represent the 2000 cumulative Gaussian functions that were fitted to the bootstrapped data. The dark grey curve represents the average cumulative Gaussian function. The vertical black line indicates the PSE of the curve. The slanted black line represents the slope with correspond to the JND of the curve. The black square is the temporal discrimination threshold. Right side: The symbols and grey lines depict the average and 95% confidence intervals for the TDT (top), PSE (middle) and JND (bottom).

4. Results

4.1. Individual participant analysis

Figure 2 shows the data, the cumulative Gaussian fit and fits to the bootstrapped data for two representative participants (P1 and P2). The participants have identical TDT values (65 ms) but different PSE (P1: 63.11 ms and P2:48.38 ms) and JND (P1: 9.98 ms and P2: 22.09 ms) parameters to their cumulative Gaussian fits. Furthermore, the 95% confidence intervals enable the statistical comparison and reveal statistical differences between the participants PSE and JND parameters (figure 2, right). Six of the 78 participants violated the goodness of fit criteria.

4.2. Parameter relationship

To investigate the relationship between the TDT values and the PSE and JND values, the data were submitted to linear

regression analyses. The results showed a significant relationship between the TDT values and the PSE, $\beta=0.62 \pm 0.062$, $t(76)=9.976$, $p<0.001$ with an explained variance of $r=0.753$, $F(1, 76)=299.528$, $p<0.001$ (figure 3, left).

The results showed a significant relationship between the TDT values and the JND values for the controls, $\beta=0.28 \pm 0.051$, $t(76)=5.474$, $p<0.001$ with an explained variance of $r=0.532$, $F(1, 76)=29.965$, $p<0.001$ (figure 3, middle). The JND values and the PSE values of the psychometric have no significant relationship with a Beta weight of -0.031 ± 0.179 , $p=0.861$ and an explained variance of $r=-0.20$, $F(1, 76)=0.031$ (figure 3, right). This would suggest that the PSE and JND values of the psychometric represent different aspects of the temporal discrimination task. A regression analysis of the sum of the PSE and JND with the TDT showed an almost one to one correspondence with $\beta=0.96 \pm 0.044$, $t(76)=22.068$, $p<0.001$

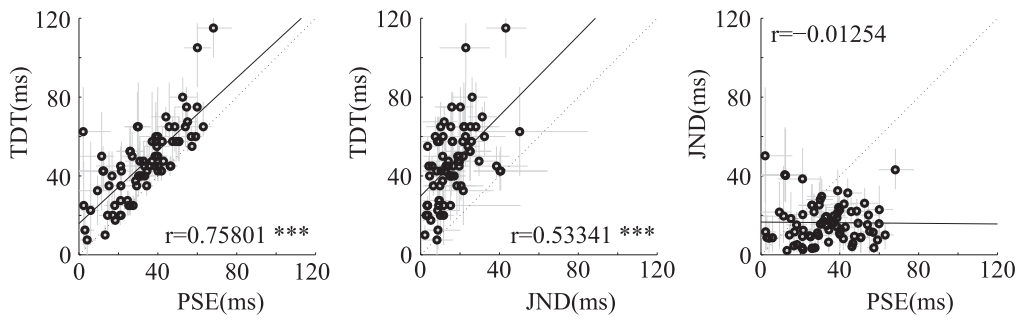


Figure 3. Scatterplot of TDT, PSE and JND values. The circles represent participant data. Error bars represent 95% bootstrapped confidence intervals. The line indicates the best fit of the data. The dashed line indicates the ideal one to one prediction for the relationship of the PSE and JND with the TDT and the Weber law for the relationship with the PSE and JND.

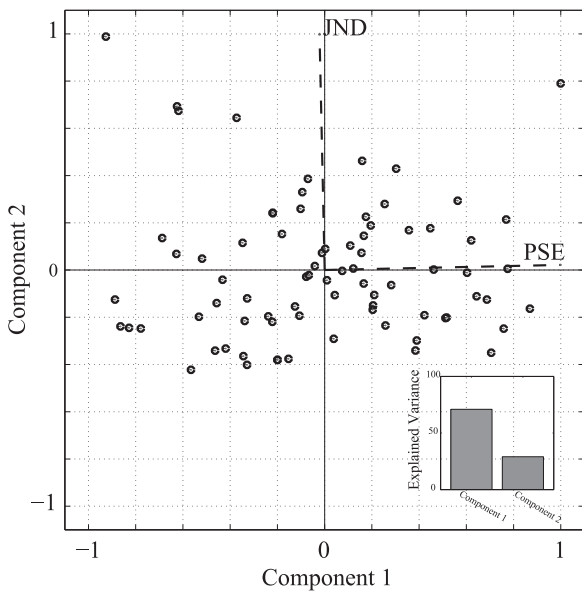


Figure 4. Principle component decomposition of the PSE and JND data. The dashed lines indicate the PSE and JND axis. The insert shows the variance explained by each component.

with an explained variance of $r=0.865$, $F(1, 76)=485.996$, $p<0.001$. This fit is not statistically different from the ideal prediction of $TDT = JND + PSE$.

To further investigate the relationship between the PSE and JND we conducted a principle component analysis. The resulting axis of the components aligned with the PSE and slope axis (figure 4). Component 1 explained 70% of the data and component 2 explained the remaining 30% (figure 4, insert). This further supports the argument that the TDT represents a combination of two independent mechanisms.

4.3. Group comparison

The data were subdivided by age into two groups, 18–35 yr and 36–65 yr (table 1 and figure 5).

The groups’ data were then submitted to unpaired *t* tests to investigate and age related differences. The analysis revealed no statistical differences between the groups for the TDT values ($t_{76}=-1.95$, $p=0.056$) and JND values ($t_{76}=0.0373$, $p=0.95$) but did reveal a statistical difference for the PSE parameter ($t_{76}=-2.55$, $p<0.0167$).

Table 1. The raw values with standard deviations (ms).

GROUP	18–35 yr	36–65 yr	<i>p</i>
<i>N</i>	41	37	
Males	24	19	
TDT (ms)	42.6 (16.7)	50.9 (16.6)	0.056
PSE (ms)	28.8 (15.6)	37.7 (15.1)	0.0126*
JND (ms)	16.6 (11.2)	16.6 (9.1)	0.95

5. Discussion

This study describes an analysis method to quantify the TDT, which has been postulated to be an endophenotype for AOIFD. The method presented here fit the TDT data with a cumulative Gaussian to extract the PSE and JND terms which represent different facets of temporal discrimination. To further strengthen the case for the TDT as an endophenotype the individual participant data we submitted to a non-parametric bootstrap procedure to define 95% confidence intervals on the extracted parameters. In a previous paper from our group, both the headset method presented here, and the standard ‘table top’ method for acquiring TDTs, yielded highly similar values within participants, illustrating the reproducibility of the acquisition method (Molloy *et al* 2014). The new acquisition headset enables the collection of data in any location, vital when assessing patients and family members living at a distance from the laboratory.

6. Fitting method

To further explore the individual participant results, the data were fitted to a cumulative Gaussian to extract both a PSE and JND term. The PSE and JND of the cumulative Gaussian correlated with the standard calculation of the TDT; thus the new analysis provides similar results without loss of information. The JND value did not correlate with the PSE which suggests that they represent different dimensions of the TDT value. This result was further explored using principal component analysis of the data which showed that the primary component aligned with the PSE axis and the second component aligned with the JND axis. This strengthens the case that the PSE and JND are independent and represent different

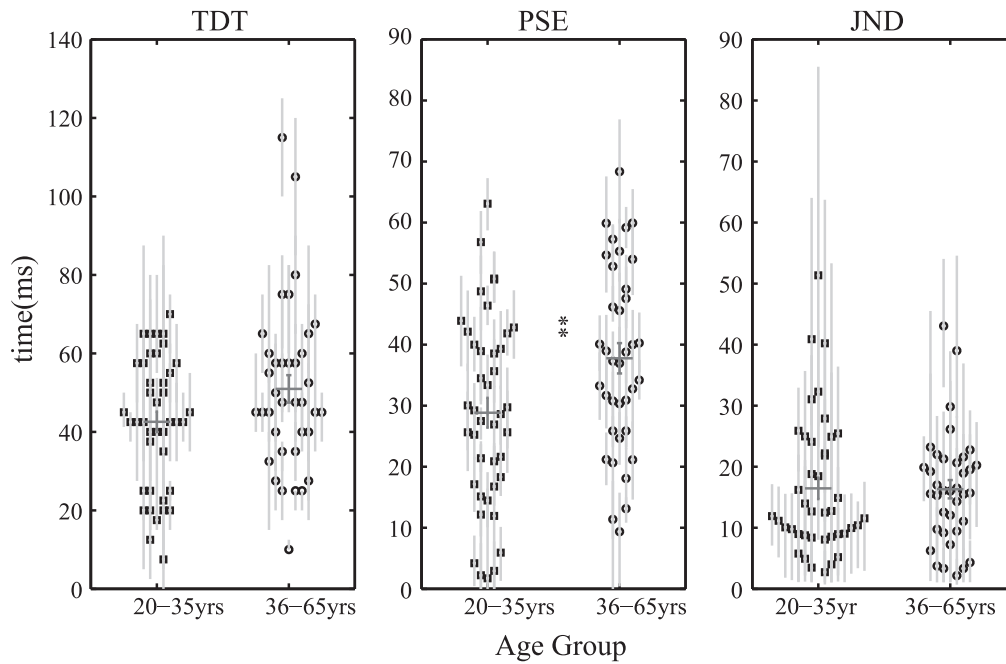


Figure 5. Illustrating the TDT (left), PSE (middle) and JND (right) for each participant divided in two groups aged 20–35 yr (squares) and 36–65 yr (circles). Error bars represent the 95% bootstrapped confidence intervals.

facets of the temporal discrimination process. An interesting note from our results is that the PSE and JND did not observe Weber’s law, which states that the variance should increase as a function of the mean (Fechner 1860); even if participants have an abnormal TDT it does not automatically imply that they have more variable responses.

By dividing the participants into two age groups we were able to investigate the relationship of age and temporal discrimination. The analysis revealed a statistical difference in the PSE values across the groups, which was only trending for the TDT values. Thus the PSE value represents a more sensitive measure of temporal discrimination, and will be of use in demonstrating differences between control and clinical groups. Furthermore, the two groups had highly similar JND values thus suggesting that the differences between the groups are due to a shift in the detection threshold and not due to less reliable differentiation of stimuli due to age.

Another benefit to fitting the response data as opposed to the standard analysis method, which requires the participant to indicate ‘different’ (indicating perceived as being asynchronous) three consecutive times, is that it provides the opportunity of freeing the methodology from the consecutive presentation of stimuli.

This would result in two immediate benefits: (1) participants would be less able to learn the order of stimulus, which is a concern when conducting multiple tests and may lead to a bias in the fitting method. (2) It would enable the use of adaptive testing procedures in the future, as the data can be fitted to curves which would shorten the time to determine each participant’s TDT (Treutwein 1995), minimizing participant fatigue and practice effects which can be an issue when acquire data from clinical populations.

6.1. Bootstrapped confidence intervals

The standard method of a single value cut-off does not represent the variability of the data and could result in false positive classifications. Therefore we further extended the current TDT analysis using a non-parametric bootstrapping method to calculate individual participant 95% confidence intervals of both the classical summary TDT analysis and the parameters of the cumulative Gaussian fit. The confidence intervals can be used to strengthen the case for normal or abnormal temporal discrimination values by enabling the statistical comparison of single participant data with the group data. While the analysis is able to construct 95% confidence intervals of the classic TDT analysis, the distribution was restricted to discrete steps due to calculation method. This also resulted in larger confidence intervals for the TDT than the PSE values and hence would not be as sensitive to statistical differences.

Another benefit of the confidence intervals is they allow statistical comparison at a single participant level (Butler *et al* 2011), this is critical when investigating biomarkers for rare diseases as group comparisons are not possible (Andrade *et al* 2014). Here we illustrated this using two representative participants’ data with identical TDT values but the analysis revealed statistically different PSE and JND values. Differences between control participants is of interest when investigating an endophenotype as it illustrates the sensitivity of the measure and that the data is a continuum. This is important as we hypothesise that abnormal temporal discrimination in unaffected relatives is a mediational endophenotype and probably a marker of gene carriage in these individuals. It may also indicate pathogenic mechanisms not obvious from the phenotype (Hutchinson *et al* 2014).

Here, a non-parametric bootstrapping method was implemented to estimate confidence intervals on both the

classical TDT method and the parameters of the psychometric function. Other methods such as parametric bootstrapping or Bayesian methods should be considered when fitting the confidence intervals of the psychometric as they have been shown to result in more accurate approximations (Wichmann and Hill 2001a, Wichmann and Hill 2001b, Kuss *et al* 2005, Frund *et al* 2011).

6.2. Future directions

In future work this method will be applied to clinical groups that have abnormal temporal discrimination such as writer's cramp (Fiorio *et al* 2003), blepharospasm (Fiorio *et al* 2008), Parkinson's disease (Artieda *et al* 1992, Lee *et al* 2005) and multiple system atrophy (Lyoo *et al* 2007). The JND and PSE values extracted from the fit may be useful in the future work to delineate differences in clinical populations; an abnormal TDT might be due to a (1) higher variability in the perception of temporal discrimination which would be represented as higher JND values or (2) that the patients have a shift in their PSE but exhibit similar variability to the controls or (3) a combination of both.

7. Conclusion

The aim of this study was to assess an analysis method to reliably measure TDT in a large population and investigate changes in TDT within participants and groups. The unified analysis and data acquisition (Molloy *et al* 2014) will enable the comparison and collation of data from different research groups and across clinical populations with the possibility of examining different facets of temporal discrimination processing.

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