NOTE

A comparison of stimulus presentation methods in temporal discrimination testing

IOP Publishing | Institute of Physics and Engineering in Medicine Physiological Measurement

Physiol. Meas. **38** (2017) N57–N64 doi:10.1088/1361-6579/38/2/N57

Note

A comparison of stimulus presentation methods in temporal discrimination testing

Eavan M Mc Govern[1,2,3], John S Butler[3,4], Ines Beiser[1,2], Laura Williams[1,2], Brendan Quinlivan[3], Shruti Narasiham[3], Rebecca Beck[3], Sean O'Riordan[1,2], Richard B Reilly[3,5] and Michael Hutchinson[1,2]

[1] Department of Neurology, St. Vincent's University Hospital, Dublin, Ireland
[2] School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland
[3] Trinity Centre for Bioengineering, Dublin, Ireland
[4] School of Mathematical Sciences, Dublin Institute of Technology, Dublin, Ireland
[5] School of Medicine Trinity College Dublin, The University of Dublin, Dublin, Ireland

E-mail: eavanmcgov@hotmail.com and e.mcgovern@svuh.ie

Received 13 July 2016, revised 7 October 2016
Accepted for publication 1 November 2016
Published 18 January 2017

Abstract

The temporal discrimination threshold (TDT) is the shortest time interval at which an individual detects two stimuli to be asynchronous (normal = 30–50 ms). It has been shown to be abnormal in patients with disorders affecting the basal ganglia including adult onset idiopathic focal dystonia (AOIFD). Up to 97% of patients have an abnormal TDT with age- and sex-related penetrance in unaffected relatives, demonstrating an autosomal dominant inheritance pattern. These findings support the use of the TDT as a pre-clinical biomarker for AOIFD. The usual stimulus presentation method involves the presentation of progressively asynchronous stimuli; when three sequential stimuli are reported asynchronous is taken as a participant's TDT. To investigate the robustness of the 'staircase' method of presentation, we introduced a method of randomised presentation order to explore any potential 'learning effect' that may be associated with this existing method. The aim of this study was to investigate differences in temporal discrimination using two methods of stimulus presentation. Thirty healthy volunteers were recruited to the study (mean age 33.73 ± 3.4 years). Visual and tactile TDT testing using a staircase and randomised method of presentation order was carried out in a single session. There was a strong relationship between the staircase and random method for TDT values. This observed consistency between testing methods suggests that the existing experimental approach is a robust method

of recording an individual's TDT. In addition, our newly devised randomised paradigm is a reproducible and more efficient method for data acquisition in the clinic setting. However, the two presentation methods yield different absolute TDT results and either of the two methods should be used uniformly in all participants in any one particular study.

Keywords: temporal discrimination, random, usual, Gaussian model, adult onset dystonia

(Some figures may appear in colour only in the online journal)

Introduction

The temporal discrimination threshold (TDT) is a measure of the point at which an individual determines two sensory stimuli to be asynchronous (normal 30–50 ms) (Kimmich *et al* 2011). It has been shown to be abnormal in neurological movement disorders affecting the basal ganglia including multiple system atrophy, Parkinson's Disease and adult onset idiopathic focal dystonia (AOIFD) (Lyoo *et al* 2007, Scontrini *et al* 2009, Bradley *et al* 2010, Rocchi *et al* 2013, Conte *et al* 2014, Kimmich *et al* 2014). Focal lesions affecting the basal ganglia may also result in abnormalities of temporal discrimination (Lacruz *et al* 1991), whereas lesions interrupting peripheral sensory pathways do not appear to affect temporal discrimination (Green *et al* 1961). Functional MRI studies (Rao *et al* 2001, Pastor *et al* 2006) indicate that the basal ganglia play an important role in temporal discrimination of sensory stimuli. Abnormal TDTs are found in non-manifesting carriers in DYT1-related dystonia and PINK1-related parkinsonism (Fiorio *et al* 2007, 2008); as such an abnormal TDT is considered to be an endophenotype, a marker of non-manifesting gene carriage. AOIFD is an autosomal dominant condition with reduced penetrance (Waddy *et al* 1991, Leube *et al* 1997, Defazio *et al* 2013); endophenotypes are useful because in less than 1% of cases of AOIFD a genetic cause can be determined. Up to 97% of patients with AOIFD have an abnormal TDT with age-related penetrance in unaffected relatives demonstrating autosomal dominant inheritance (Bradley *et al* 2010, Kimmich *et al* 2011, 2014). These findings support the use of the TDT as an endophenotype, for AOIFD (Stamelou *et al* 2012, Kimmich *et al* 2014).

Despite the expanding literature on this endophenotype, little work has been done to examine or standardise the experimental approach for examining temporal discrimination. To bridge this gap and standardise the experimental protocol, we set out to compare different methodological approaches of stimulus presentation. Our current experimental protocol (staircase stimulus presentation) uses two progressively-asynchronous stimuli (visual or tactile) presented to an individual; the TDT is taken as the first of three consecutively-reported asynchronous stimuli (Kimmich *et al* 2011). Both stimuli (visual and tactile) are tested four times on each side (left and right), resulting in a total of 16 trials. The time at which an individual determines two stimuli to be asynchronous can vary considerably, consequently, the experiment duration is not consistent across participants. Non-randomised, progressively asynchronous (staircase) presentation of stimuli may be perceived to contribute to a potential learning effect. However, several studies have demonstrated that TDT values do not statistically vary across repeated experimental sessions; thus suggesting that the staircase method is not affected by a learning effect (Conte *et al* 2016, 2010). To further explore this issue, we devised a method of randomised presentation order of stimuli that was uniform in test duration. In so doing, we aimed to develop an alternative, reproducible, efficient experimental

paradigm to remove participant subjectivity, enhance standardisation and ease data acquisition in the clinical setting.

In a previous paper we expanded our analysis of temporal discrimination to fully characterise a single participant's data (Butler *et al* 2015). In this paper, we adopted this 'bootstrap' analysis and fit participant data to a cumulative Gaussian psychometric function to extract the TDT, point of subjective equality (PSE) and the just noticeable difference (JND) for each participant. The PSE corresponds to the mean value of the Gaussian and the JND is proportional to the standard deviation of this function. We previously demonstrated that the PSE represents the most sensitive measure of temporal discrimination (Butler *et al* 2015); thus the PSE was of particular interest in comparing different methods of stimulus presentation.

Aims

(i) To investigate any differences that exist in temporal discrimination values using two methods of stimulus presentation (staircase and randomised). (ii) To devise a reproducible, efficient, randomised approach to enhance standardisation of the experimental protocol and to facilitate data acquisition in the clinical setting.

Participants and methods

Participants

Thirty, healthy volunteers (15 women) were recruited. Exclusion criteria included current or past history of any neurological disorder. The mean age of study participants was 33.73 years (SD $\pm$ 3.4 years). The study was approved by the Medical Research Ethics Committee at St Vincent's University Hospital. Participants were randomised as to the order of testing (staircase or randomised).

Staircase TDT stimulus presentation

Visual and tactile TDT testing using the staircase method of stimulus presentation was carried out in a single session, in a sound-proofed, darkened room. This method has been previously described (Kimmich *et al* 2011). Briefly, this method involves presentation of progressively asynchronous stimuli to an individual. Participants were tested for two modalities: (i) a visual task (two flashing light-emitting diodes); and (ii) a tactile task (non-painful electrical stimulation of the index and middle finger). Stimuli were presented at 5 s intervals with asynchronicity incrementally separated in 5 ms steps. Participants were instructed that each pair of stimuli will either occur at the same time, i.e. perceived as one stimulus, or they will be separated in time so that one stimulus occurs earlier than the other, i.e. perceived as two stimuli distinct from one another. For each pair of stimuli, participants responded with a one-word response, 'same'—the stimuli are perceived as one stimulus, or 'different'—the stimuli are perceived as two stimuli. The trial ended when the participant reported on three consecutive occasions that the pairs of white LEDs flashed asynchronously. The first of three asynchronous responses was taken as the TDT for that trial. This procedure was repeated four times on the left and right side of the body for both modalities (visual and tactile) resulting in a total of 16 runs per participant.

Random TDT stimulus presentation: Visual and tactile TDT testing was repeated in a randomised presentation order in the same session. Participants were once again tested for two

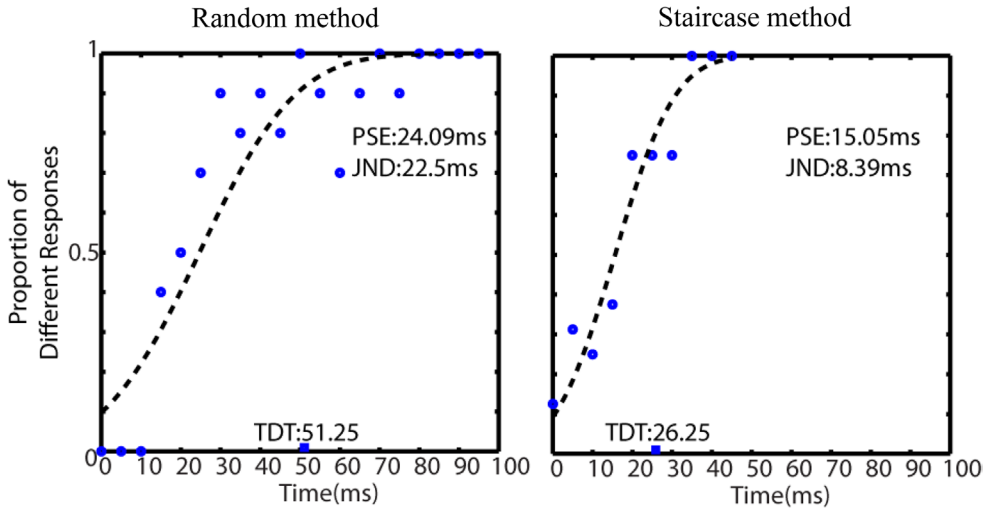

Figure 1. Data from one participant using the random and staircase method stimulus presentation during TDT acquisition. The blue circles show the proportion of perceived 'different' responses as a function of temporal asynchrony. The dashed curve represents the average cumulative Gaussian function. The blue square on the *X*-axis is the temporal discrimination threshold.

modalities. Stimuli were presented randomly, with asynchronicity varying between 0 and 100 ms, at 5 s intervals. Participants were instructed to respond 'same' or 'different' following each stimulus presentation. The random TDT is calculated in the same way as the staircase approach. However, it requires one additional step; the data is first re-arranged in sequential order. The TDT for that trial is taken as the first of three asynchronous responses. The procedure was repeated four times on the left and right side of the body for both modalities (visual and tactile) resulting in a total of sixteen runs per participant.

Statistical analysis

Temporal discrimination threshold

A participant's TDT was calculated by taking the median of four runs for each modality. The results were averaged to obtain a single-combined TDT value, expressed in milliseconds (ms).

Participant data psychometric fit

A cumulative Gaussian psychometric function was fitted to the asynchronous responses. This method of TDT data analyses has been described previously (Butler *et al* 2015). Briefly, participant responses were coded as follows; 0 = 'same' (synchronous), 1 = 'different' (asynchronous). For the staircase presentation method, the number of asynchronous responses varied across trials as each trial terminated when a participant responded 'different' on three occasions. Responses were assumed to be different following termination of the run and the data was fitted to longest run across all participants. Participant asynchronous responses for the random method were also fitted to this psychometric function. The responses for both methods were averaged and plotted as a function of stimulus asynchrony and the mean and slope were extracted for each participant (figure 1).

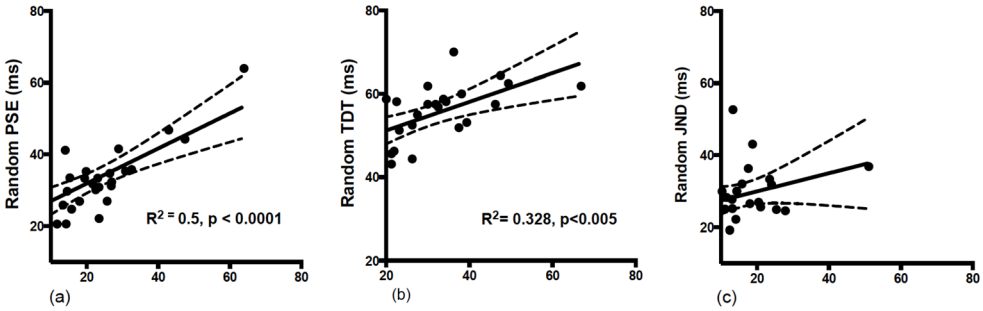

Figure 2. (a)–(c) Scatterplots of the PSE, TDT and JND values for the 30 participants determined by two different stimulus presentation techniques (staircase and random) showing the relationship between the; (a) PSE(random) and PSE(staircase), (b) TDT(random) and TDT(staircase), (c) JND(random) and JND(staircase) (PSE: perceived subjective equality. TDT: temporal discrimination threshold. JND: just noticeable difference).

The PSE is the cumulative response of 0.5—the point at which an individual is equally likely to respond 'same' or 'different' to a stimulus. The slope of the curve represents the standard deviation of the Gaussian and is called the JND; this represents how sensitive an individual is to change around the PSE.

Comparison of staircase method and randomised method: To investigate the relationship between the two testing methods three correlation analyses were carried out:

(1) PSE(staircase) versus PSE(random); (2) TDT(staircase) versus TDT(random); (3) JND(staircase) versus JND(random). The *F*-values, mean squared error (MSE), *R*-squared values and corresponding *p*-values are reported along with 95% confidence intervals, *t*-values, and *p*-values for the intercept, and Beta value for the linear fit.

Results

Thirty participants completed the study. The mean age of study participants was 33.7 years (SD $\pm$ 3.4 years). Male and female participants were age-matched and equal in number. The mean values for the staircase method were: TDT = 30.57 ms, PSE = 23.38 ms, JND = 15.95 ms. The mean values for the random method were: TDT 55.08 ms, PSE 33.89 ms, JND 28.76 ms.

To investigate the relationship between the two presentation techniques (staircase and random) the PSE, TDT and JND data were submitted to linear regression analysis. For the PSE, there was a significant relationship between the PSE(staircase) and PSE (random); PSE (random) explained a significant amount of the variance in the PSE(staircase) $\{F\,(1,25) = 23.728$, MSE = 1025.773, $p < 0.0001$, $R^2 = 0.487$, $R^2_{\text{ADJUSTED}} = 0.466\}$ with a significant intercept 22.064, $\{t(26) = 8.265$, $p < 0.001$; 95% CI (16.566, 27.562)$\}$, a significant Beta = 0.490, $\{t(26) = 4.871$, $p < 0.0001$; 95% CI (0.283, 0.697)$\}$ (figure 2(a)). For the TDT, the results also showed a significant relationship between the TDT(staircase) and TDT(random); TDT(random) explained a significant amount of the variance in the TDT(staircase) $\{F\ (1,25) = 12.208$, MSE = 463.334, $p < 0.005$, $R^2 = 0.328$, $R^2_{\text{ADJUSTED}} = 0.301\}$ with a significant intercept 44.32, $\{t(26) = 13.699$, $p < 0.001$; 95% CI (37.657, 50.983)$\}$, a significant Beta = 0.344, $\{t(26) = 3.494$, $p < 0.005$; 95% CI (0.141, 0.547)$\}$ (figure 2(b)). For the JND, there was no significant relationship between the JND(random) and the JND(staircase)

$\{F\ (1,\ 25) = 2.22,\ \text{MSE} = 147.7,\ p = 0.149,\ R^2 = 0.082,\ R^2_{\text{ADJUSTED}} = 0.045\}$ with a significant intercept 24.878, $\{t(26) = 7.962,\ p < 0.001;\ 95\%\ \text{CI}\ (18.443,\ 31.3)\}$, a significant Beta = 0.252, $\{t(26) = 1.490,\ p = 0.149;\ 95\%\ \text{CI}\ (-0.096,\ 0.601)\}$ (figure 2(c)).

Discussion

We have demonstrated a significant relationship between the staircase and random methods of stimulus presentation in the assessment of temporal discrimination by both the TDT and PSE measures. The strength of this observed relationship suggests that any potential 'learning effect' is consistent across participants and highlights the importance of maintaining consistency in experimental technique selection. Neurophysiological laboratories may establish normal TDT and PSE values in healthy control participants using either technique provided that the 'staircase' or 'randomised' approach is uniformly used across participants. The same technique used to generate these values should also be used when testing patients. The existing staircase method is a robust approach for assessing temporal discrimination; multi-session study designs have demonstrated consistent results across repeated experiments (Conte *et al* 2016, 2010). This suggests that the staircase method is unaffected by a potential learning effect. Furthermore, the temporal discrimination task requires subject familiarity with the procedure; all participants, before formal assessment of the TDT, should have an introductory trial to make them at ease with the test procedure.

The staircase method yields consistently shorter values for the TDT (by 25 ms) and the PSE (by 10 ms) than the random method of presentation. Some of this variability may be due to potential learning effects, not consistent between subjects. The newly devised randomised approach presents a technique potentially less susceptible to such confounders. In addition, the randomised presentation is a more efficient approach for data acquisition; an important consideration in attempting to minimise participant fatigue and facilitate increased data collection in the clinical environment. Similarly, devices with a starting procedure individualised to a participant's threshold may shorten the task to a similar extent. Irrespective of the experimental technique, our results emphasise the importance of maintaining uniformity in experimental technique selection.

Another important consideration in temporal discrimination testing is precise data analysis; a more detailed approach may enhance our understanding of this endophenotype. We have previously demonstrated that the PSE is the most sensitive measure of temporal discrimination (Butler *et al* 2015). Therefore, this value is particularly important when comparing different groups of participants and the effects of age and sex (Williams *et al* 2015). The JND represents another facet of the temporal discrimination process (Butler *et al* 2015) and is perhaps a less sensitive measure of the temporal discrimination process, reflected in the absence of a significant relation observed for the JND values measured by the two techniques.

Evaluation of diagnostic tests and investigations should involve careful comparison of existing methodology to refine and improve techniques currently in use (Belavý *et al* 2015, Saknite *et al* 2016, Shehab *et al* 2016); which in turn will enhance diagnostic yield and accuracy. This approach should also be applied when appraising preclinical biomarkers. The preclinical (endophenotype) state represents a window of opportunity for potential-disease-modifying interventions to delay or halt disease onset (Fiandaca *et al* 2014). Endophenotypes improve our understanding of underlying pathobiologic networks underpinning disease (Hutchinson *et al* 2013). Identification of dysregulated pathways can form targets for therapeutic interventions (Premi *et al* 2016, Rae *et al* 2016). Therefore, precision testing is vital when employing preclinical biomarkers (Kimmich *et al* 2011, Bradley *et al* 2012, Conte *et al* 2014).

Conclusion

Our results have demonstrated a strong relationship for TDT values between the staircase and randomised stimulus-presentation methods. We have devised a novel and time-efficient randomised stimulus presentation protocol for TDT acquisition, which may facilitate data collection. Irrespective of the experimental technique, our results emphasise the importance of maintaining uniformity in experimental technique selection. This will ensure reproducible data acquisition amongst AOIFD patients and their relatives; which may in turn enhance our understanding of this condition.

Acknowledgments

This research was supported by grants from Dystonia Ireland, the Irish Institute for Clinical Neuroscience, the Foundation for Dystonia Research (Belgium) and the Trinity Centre for BioEngineering.

Financial disclosures (previous 12 months)

Eavan McGovern, John Butler, Ines Beiser, Laura Williams, Brendan Quinlivan, Shruti Narasiham, Rebecca Beck and Richard Reilly have no funding sources, financial disclosures or conflict of interests to declare.

Michael Hutchinson: serves as associate editor of the Multiple Sclerosis Journal, has received speaker's honoraria from Biogen-Idec, Bayer-Schering and Novartis and receives research grants from Dystonia Ireland, the Health Research Board of Ireland (CSA-2012-5), Foundation for Dystonia Research (Belgium) and the Irish Institute of Clinical Neuroscience. Sean O'Riordan reports receiving a speaker's honorarium from Abbvie.

Ethics statement

Written informed consent was obtained from all participants. The study was approved by the Medical Research Ethics Committee at St Vincent's University Hospital.

References

Belavý D L, Miokovic T, Armbrecht G and Felsenberg D 2015 Evaluation of neck muscle size: long-term reliability and comparison of methods *Physiol. Meas.* **36** 503–12

Bradley D, Whelan R, Walsh R, O'Dwyer J, Reilly R, Hutchinson S, Molloy F and Hutchinson M 2010 Comparing endophenotypes in adult-onset primary torsion dystonia *Mov. Disorders* **25** 84–90

Bradley D *et al* 2012 Temporal discrimination thresholds in adult-onset primary torsion dystonia: an analysis by task type and by dystonia phenotype *J. Neurol.* **259** 77–82

Butler J S, Molloy A, Williams L, Kimmich O, Quinlivan B, O'Riordan S, Hutchinson M and Reilly R B 2015 Non-parametric bootstrapping method for measuring the temporal discrimination threshold for movement disorders *J. Neural Eng.* **12** 46026

Conte A, Leodori G, Ferrazzano G, De Bartolo M I, Manzo N, Fabbrini G and Berardelli A 2016 Somatosensory temporal discrimination threshold in Parkinson's disease parallels disease severity and duration *Clin. Neurophysiol.* **127** 2985–9

Conte A, Modugno N, Lena F, Dispenza S, Gandolfi B, Iezzi E, Fabbrini G and Berardelli A 2010 Subthalamic nucleus stimulation and somatosensory temporal discrimination in Parkinson's disease *Brain* **133** 2656–63

Conte A, Rocchi L, Ferrazzano G, Leodori G, Bologna M, Li Voti P, Nardella A and Berardelli A 2014 Primary somatosensory cortical plasticity and tactile temporal discrimination in focal hand dystonia *Clin. Neurophysiol.* **125** 537–43

Defazio G, Jankovic J, Giel J L and Papapetropoulos S 2013 Descriptive epidemiology of cervical dystonia *Tremor Other Hyperkinet. Mov.* **3**

Fiandaca M S, Mapstone M E, Cheema A K and Federoff H J 2014 The critical need for defining preclinical biomarkers in Alzheimer's disease *Alzheimer's Dementia* **10** S196–212

Fiorio M *et al* 2007 Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? *Brain* **130** 134–42

Fiorio M *et al* 2008 Subclinical sensory abnormalities in unaffected PINK1 heterozygotes *J. Neurol.* **255** 1372–7

Green J B, Reese C L, Pegues J J and Elliott F A 1961 Ability to distinguish two cutaneous stimuli separated by a brief time interval *Neurology* **11** 1006–10

Hutchinson M *et al* 2013 The endophenotype and the phenotype: temporal discrimination and adult-onset dystonia *Mov. Disorders* **28** 1766–74

Kimmich O, Bradley D, Whelan R, Mulrooney N, Reilly R B, Hutchinson S, O'Riordan S and Hutchinson M 2011 Sporadic adult onset primary torsion dystonia is a genetic disorder by the temporal discrimination test *Brain* **134** 2656–63

Kimmich O *et al* 2014 Temporal discrimination, a cervical dystonia endophenotype: penetrance and functional correlates *Mov. Disorders* **29** 804–11

Lacruz F, Artieda J, Pastor M A and Obeso J A 1991 The anatomical basis of somaesthetic temporal discrimination in humans *J. Neurol. Neurosurg. Psychiatry* **54** 1077–81

Leube B, Kessler K R, Goecke T, Auburger G and Benecke R 1997 Frequency of familial inheritance among 488 index patients with idiopathic focal dystonia and clinical variability in a large family *Mov. Disorders* **12** 1000–6

Lyoo C H, Seung Y L, Tae J S and Myung S L 2007 Abnormal temporal discrimination threshold in patients with multiple system atrophy *Mov. Disorders* **22** 556–9

Pastor M A, Macaluso E, Day B L and Frackowiak R S J 2006 The neural basis of temporal auditory discrimination *Neuroimage* **30** 512–20

Premi E *et al* 2016 Looking for neuroimaging markers in frontotemporal lobar degeneration clinical trials: a multi-voxel pattern analysis study in granulin disease *J. Alzheimers Dis.* **51** 249–62

Rae C L *et al* 2016 Atomoxetine restores the response inhibition network in Parkinson's disease *Brain*

Rao S M, Mayer A R and Harrington D L 2001 The evolution of brain activation during temporal processing *Nat. Neurosci.* **4** 317–23

Rocchi L, Conte A, Nardella A, Li Voti P, Di Biasio F, Leodori G, Fabbrini G and Berardelli A 2013 Somatosensory temporal discrimination threshold may help to differentiate patients with multiple system atrophy from patients with Parkinson's disease *Eur. J. Neurol.* **20** 714–9

Saknite I, Zavorins A, Jakovels D, Spigulis J and Kisis J 2016 Comparison of single-spot technique and RGB imaging for erythema index estimation *Physiol. Meas.* **37** 333–46

Scontrini A, Conte A, Defazio G, Fiorio M, Fabbrini G, Suppa A, Tinazzi M and Berardelli A 2009 Somatosensory temporal discrimination in patients with primary focal dystonia *J. Neurol. Neurosurg. Psychiatry* **80** 1315–9

Shehab H, Desouza E D, O'Meara J, Pejović-Milić A, Chettle D R, Fleming D E B and McNeill F E 2016 Feasibility of measuring arsenic and selenium in human skin using *in vivo* x-ray fluorescence (XRF)—a comparison of methods *Physiol. Meas.* **37** 145–61

Stamelou M, Edwards M J, Hallett M and Bhatia K P 2012 The non-motor syndrome of primary dystonia: clinical and pathophysiological implications *Brain* **135** 1668–81

Waddy H M, Fletcher N A, Harding A E and Marsden C D 1991 A genetic study of idiopathic focal dystonias *Ann. Neurol.* **29** 320–4

Williams L J, Butler J S, Molloy A, McGovern E, Beiser I, Kimmich O, Quinlivan B, O'Riordan S, Hutchinson M and Reilly R B 2015 Young women do it better: sexual dimorphism in temporal discrimination *Front. Neurol.* **6** 1–8