Practice Does Not Make Perfect: Temporal Discrimination in Musicians With and Without Dystonia

Musician's dystonia (MD), characterized by loss of voluntary control while playing an instrument, is a phenotype of adult-onset isolated focal dystonia (AOIFD).[1] Abnormal sensory processing is a common finding in AOIFD[2]; the temporal discrimination threshold (TDT) is a marker of this.[3] TDT is a measure of the shortest time interval at which 2 stimuli are perceived as asynchronous. It is abnormally elevated in non-MD phenotypes of AOIFD.[3,4] Abnormal TDTs occur less frequently in MD.[3]

Musicians perform better than nonmusicians at various timing tasks.[5] However, compared with healthy musicians, MD subjects exhibit intact timing abilities.[6] We hypothesized that the nonmusician control subjects might have masked an underlying abnormality in TDTs in the MD subjects, which could be discerned on comparison with control musicians.

We hypothesized that (1) compared with a control population of healthy musicians, musicians with dystonia would have abnormal TDTs; and (2) healthy musicians would have faster, "better-than-normal" TDTs compared with healthy nonmusicians.

We measured TDTs in 20 patients with musician's dystonia (group 1), 20 healthy musicians (group 2), and 94 healthy nonmusicians (group 3) according to a method previously described.[7] Briefly, subjects were asked to report when they perceived a delay between a pair of flashing light-emitting diodes positioned on a table in front of them. Repeated trials were averaged, and Z scores were obtained for each subject. Two Z scores were derived using musician and nonmusician controls as reference populations. The number of abnormal controls in each group was assessed for significance using Fisher's exact test, with a threshold for significance of $P = 0.025$.

All subjects gave informed consent, and ethical approval was obtained for the study. All participants had normal cognition, visual acuity, and no sensory impairments or history of significant neurological conditions.

There were no significant differences in age among the 3 groups. Figure 1 plots the TDT results for subjects in each group. The MD group had a mean TDT of 47.3 milliseconds (SD, 23.3 milliseconds). The control musician group had a mean TDT of 23 milliseconds (SD, 7.3 milliseconds), and the nonmusician control group had a mean TDT of 32.9 milliseconds (SD, 15.9 milliseconds).

Using Z scores derived from nonmusician controls as the reference, only 20% of the MD group (4 of 20) was

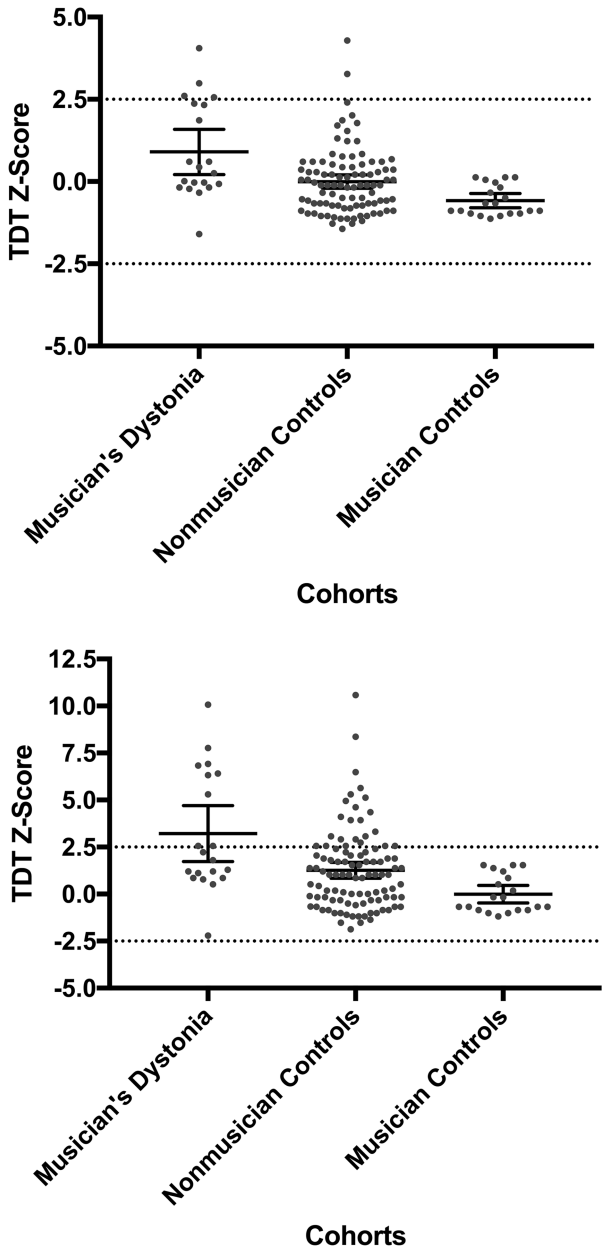

FIG. 1. Z scores based on different reference populations: two-dot plots of temporal discrimination threshold (TDT) Z scores across the 3 groups, on the left using the healthy nonmusician control participants (group 3) as the reference population (mean, 32.9 milliseconds; SD, 15.9 milliseconds) and on the right using healthy musician controls (group 2) as the reference population (mean, 23.7 milliseconds; SD, 7.3 milliseconds). The dotted lines define Z scores of ± 2.5 SDs relative to the mean of the reference population. Error bars indicate group means and the 95% confidence intervals.

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identified as having abnormal TDTs (Z score ≥ 2.5) and 2% of nonmusician controls. Fisher's exact test was not significant.

Using the musician control group as a reference, 45% of MD subjects (9 of 20) and 22% of nonmusician control subjects (21 of 94) were found to be abnormal. Fisher's exact test returned significant P values for comparisons between MD subjects and control musicians ($P < 0.001$) and between control musicians and nonmusicians ($P = 0.02$).

Our results indicate that MD subjects have significantly more abnormal TDTs compared with healthy musicians. Our musician control group and larger sample size allowed us to detect this effect that contradicts previous studies of temporal processing in MD. We also identified a significant difference in TDT between musician controls and nonmusicians, which suggests that playing an instrument improves temporal processing. Further research will be required to characterize differences in TDT within the MD cohort. ■

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Complex Genomic Rearrangement in *SPG11* Due to a DNA Replication-Based Mechanism

Spastic paraplegia type 11 (SPG11: OMIM 604360) is an autosomal-recessive complex hereditary spastic paraplegia (HSP). Intellectual disability, peripheral neuropathy, pseudobulbar involvement, and thinning of the corpus callosum are frequently observed.[1] Mutations in the gene encoding spatacsin (*SPG11*; OMIM 610844) cause SPG11.[2] Approximately 90% of disease-causing mutations in *SPG11* are nonsense, splicing, and frameshift mutations, which are detected by direct sequencing. Deletions or duplications of 1 or more exons of *SPG11* account for up to 10% of mutations and are detected by multiplex ligation probe amplification (MLPA).[3] Exonic deletions in *SPG11* have previously been shown to be caused by nonallelic homologous recombination (NAHR) mediated by *Alu* repeats.[4]

Case Report

We describe a 23-year-old woman, born to nonconsanguineous parents, who presented with episodic dystonia at 18 months. She developed a spastic gait at 6 years, which progressively worsened by age 13. She became stiff and developed bradykinesia, and her cognitive function became noticeably worse. At 17 years of age, she developed significant dysarthria and swallowing difficulties and required assistance for most activities of daily living. Physical examination revealed masked facies, bradykinesia, cogwheel rigidity, lower extremity weakness, spasticity, and extensor plantar response. Her speech, cognition, and motor function progressively worsened, and she has been wheelchair-dependent since age 20. Brain MRI revealed mild diffuse cerebral volume loss, "ears of the lynx" sign, and thin anterior corpus callosum.

Results and Discussion

Sequencing of *SPG11* revealed a previously reported heterozygous c.3664_3665insT (p.Lys1222Ilefs*15) frameshift mutation.[5] Subsequent MLPA analysis did not identify exonic deletions or duplications in genomic DNA, so analysis of *SPG11* mRNA from the patient's muscle biopsy was undertaken. Reverse transcriptase PCR (RT-PCR) was used to amplify the entire spatacsin transcript in overlapping

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