Delineating Cerebellar Mechanisms in DYT11 Myoclonus-dystonia

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ABSTRACT: Background: Recent research has highlighted the role of the cerebellum in the pathophysiology of myoclonus-dystonia syndrome as a result of mutations in the ϵ-sarcoglycan gene (*DYT11*). Specifically, a cerebellar-dependent saccadic adaptation task is dramatically impaired in this patient group.
Objectives: The objective of this study was to investigate whether saccadic deficits coexist with impairments of limb adaptation to provide a potential mechanism linking cerebellar dysfunction to the movement disorder within symptomatic body regions.
Methods: Limb adaptation to visuomotor (visual feedback rotated by 30°) and forcefield (force applied by robot to deviate arm) perturbations were examined in 5 patients with *DYT11* and 10 aged-matched controls.
Results: Patients with *DYT11* successfully adapted to both types of perturbation. Modelled and averaged summary metrics that captured adaptation behaviors were equivalent to the control group across conditions.
Conclusions: DYT11 is not characterized by a uniform deficit in adaptation. The previously observed large deficit in saccadic adaption is not reflected in an equivalent deficit in limb adaptation in symptomatic body regions. We suggest potential mechanisms at the root of this discordance and identify key research questions that need future study.

Key Words: Dystonia; DYT11; cerebellum; adaptation; ϵ-sarcoglycan

Introduction

Myoclonus-dystonia syndrome is a rare movement disorder with lightning-like myoclonic jerks, mild to moderate dystonia, and associated psychiatric abnormalities.[1] The most frequent genetic cause of myoclonus-dystonia, DYT11, is the result of loss of function mutations in the ϵ-sarcoglycan gene and is inherited in an autosomal dominant manner with incomplete penetrance.[2,3] With no overt neurodegeneration, the disease is thought to represent a functional neural disturbance across a predominantly subcortical network.[4,5] Recently there has been much attention on the role of the cerebellum within pathophysiological models for DYT11, with cerebellar involvement suggested by both animal models and human studies.[6–8]

One of the most compelling lines of research to date has been the observation that patients with DYT11 perform highly abnormally on a cerebellar oculomotor paradigm called *saccadic adaptation*.[9] In this paradigm, individuals are asked to move their eyes to a target, and the position of the target is changed just before the saccade reaches the target. This forces a corrective saccade after every target jump and after repetition adaptation occurs such that saccades become bigger or smaller depending on the direction of the jump.[10] In DYT11, the magnitude of saccadic adaptation was significantly lower, with little overlap between the range of values of adaptation obtained for DYT11 and controls with a correspondingly high effect size.[9]

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In this study, we investigated whether the observed deficit in saccadic adaptation coexists with an impairment of limb adaptation. This would take the cerebellar hypothesis a step further as it would provide a potential mechanism by which cerebellar dysfunction could contribute to poor calibration of posture and movement within symptomatic body regions. We tested 2 types of limb adaptation in the affected arms of patients with DYT11. The first, visuomotor perturbation, distorts visual feedback by 30° degrees. This shares some components with the saccadic task in that it also involves a visual perturbation yet uniquely requires updated movements of the symptomatic arms rather than the eyes.[11] The second type of adaptation examined the ability to update arm movements in response to a forcefield exerted by a robotic manipulandum, a paradigm that probes the proprioceptive system in greater isolation.[12]

Methods

A total of 5 patients with genetically proven DYT11 myoclonus dystonia were recruited from the National Hospital for Neurology and Neurosurgery (clinical details given in the Supplementary Table) and data were compared with 10 aged-matched controls (previously published)[13]. Saccadic adaptation was dramatically impaired in a previous study, and we performed a sample size calculation based on this published data's variance. A 12.7% difference between the patients' and controls' saccadic adaptation performance was noted, and the standard deviation within both groups was (over) estimated at 4%. A power of 99% (high) and the chance of type I error at $P = .05$ (standard statistical cut off) identified 3.19 subjects to be required in each group. If nonnormality is also assumed, an increase of subject numbers of 16% is generally advised, giving a requirement for 3.70 or 4 individuals in each group.[14] The group of 10 controls further increased the reliability of our findings.[15] Therefore, we believe a patient group size of 5 was large enough to detect a similar impairment in limb adaptation as observed with saccadic adaptation.

The limb adaptation task involved participants moving a cursor from a central starting position through 1 of the 4 radially located targets through the control of a robotic manipulandum (Fig. 1a). Each participant completed 5 experimental conditions in which baseline performance was assessed and then participants were examined for their ability to adapt and washout both visuomotor and forcefield perturbations (Fig. 1a). The full experimental method is detailed in the Supplementary Materials accompanying this article.

To facilitate comparison to previous studies, similar mean outcome metrics were calculated for both visuomotor and forcefield conditions: (i) late adaptation, the mean angular error during the last 40 trials of the perturbation, and (ii) error on removal was estimated by calculating the mean error during the first 8 trials once the perturbation had been removed.

To assess individual performance, we also modeled angular error using an exponential function for each for the 4 conditions (visuomotor adaptation learning and unlearning, forcefield adaptation learning and unlearning):

$$Y = a + bexp^{(-cx)}$$

where Y represents the predicted angular error, a is an estimate of the plateau of the learning curve, b is an estimate of the maximal initial error (the y-intercept), c estimates the learning index for each condition, and x is the epoch. The learning index is the percentage reduction in error for each epoch and thus can be used as a measure of the rate of adaptation and the rate of washout of perturbations. The adjusted R^2 value was calculated to analyze goodness of fit of the model.

Adaptation outcomes were compared by the Mann-Whitney U test as a result of the small sample size and the U statistic, and P value and effect size (r) are written for each comparison. A Bonferroni correction was applied when 3 model parameters were evaluated (0.05/3 = 0.016). SPSS (IBM SPSS Statistics, version 24; IBM Corp., Armonk, New York) and Matlab (R2017a; MathWorks, Natick, Massachusetts) were used for data analysis.

Results

During the baseline block, both groups made comparable and adequate reaches with no significant difference seen between groups for reaction time (control media 446.9 ms, DYT11 median 466.6 ms, $U = 22$, $P = .71$, $r = 0.09$), movement time (control median 288 ms, DYT11 median 314 ms, $U = 24$, $P = .90$, $r = 0.03$), or angular error at maximal velocity (control median 1.72, DYT11 median 2.37, $U = 20$, $P = .59$, $r = 0.15$).

Participants were then examined for their ability to adapt and washout both visuomotor and forcefield perturbations (Fig. 1b). For the visuomotor perturbation, both late adaptation (Fig. 1c, $U = 14$, $P = .18$, $r = 0.35$) and the initial error at perturbation removal (Fig. 1d, $U = 19$, $P = .46$, $r = 0.19$) were equivalent. Late adaptation (Fig. 1e, $U = 18$, $P = .44$, $r = 0.22$) and initial error (Fig. 1f, $U = 20$, $P = .59$, $r = 0.16$) were also equivalent for the forcefield perturbation.

In addition, we modeled adaptation data for each experimental condition. All individuals met the requirement that R^2 was greater than 0.4 (ie, model explained

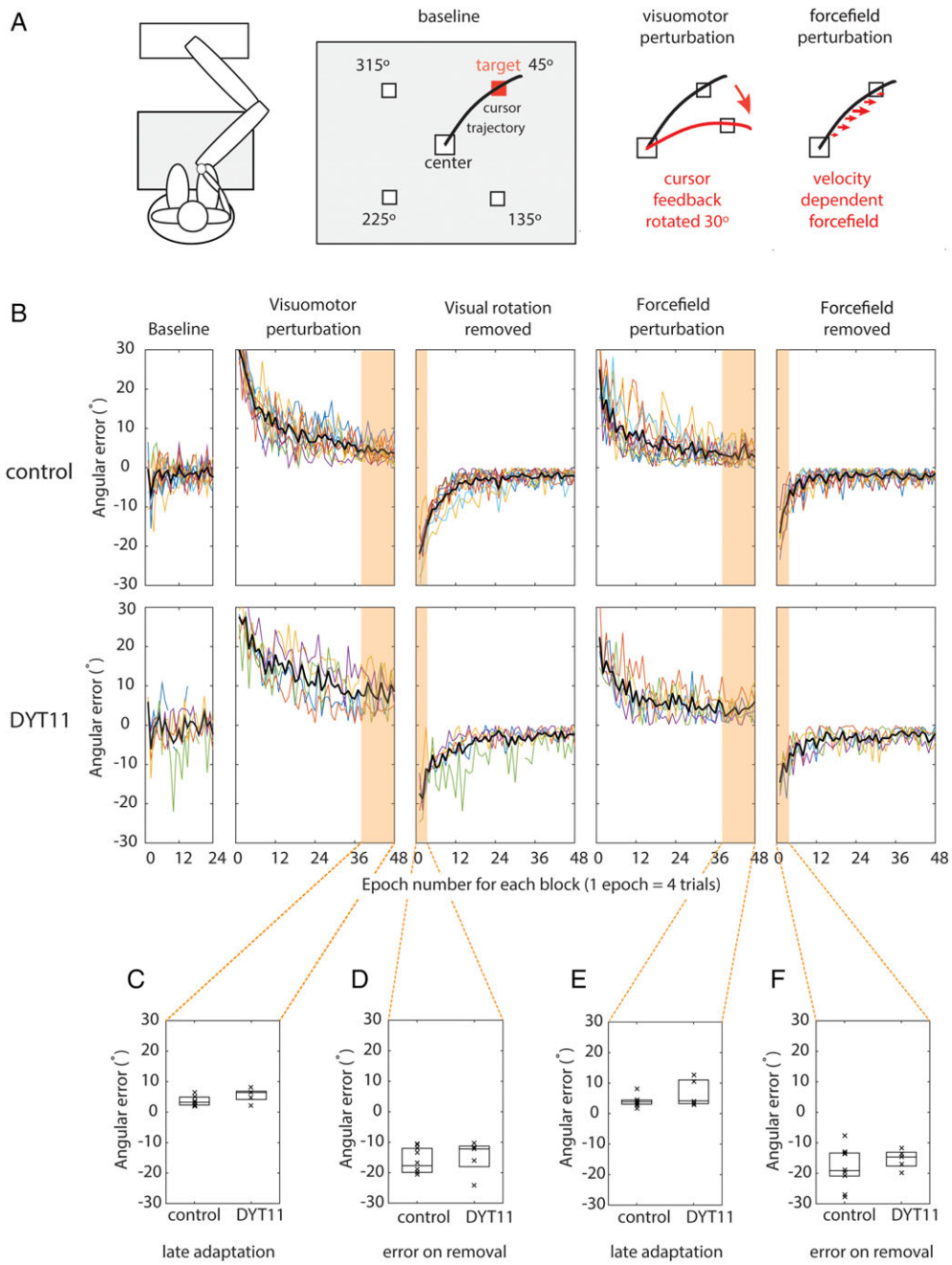

FIG. 1. Patients with DYT11 adapt comparably to healthy controls in response to visuomotor and forcefield perturbations. (A) Experimental setup and illustration of the 2 types of adaptation tested. In the visuomotor condition, visual feedback was distorted by 30° in the clockwise (positive) or anticlockwise (negative) direction. The forcefield condition consisted of a rightward (positive) or leftward (negative) velocity dependent force applied to the robotic arm during movement (3N/[m/s]). (B) Individual's adaptation behavior is indicated by colored lines, and the group mean is shown by a thicker black line. At both the individual and group levels, DYT11 patients adapted to both types of perturbation (gradually reducing angular error as the perturbation is ongoing). When the perturbation is removed, error in the opposite direction is seen and the perturbation is gradually unlearnt. (C) To facilitate comparison to previous papers we quantified mean adaptation at 2 time points; the last 40 trials of the perturbation (late adaptation) and the first 8 trials after the perturbation ceased (error on removal). Boxplots show individual data points (crosses), and the median and interquartile ranges outline the boxplot. Patients with DYT11 were equally able to adapt to both visuomotor and forcefield perturbations and error on removal of both perturbations was equivalent.

more than 40% of variation, no exclusions). The 3 parameters that described the fitted function (plateau, maximal error, learning rate) were also found to be equivalent across groups (Fig. 2, statistics shown in Table 2 of the Supplementary Material).

Collectively these results suggest that the effect observed in DYT11 for saccadic adaptation does not translate into a corresponding deficit in limb adaptation in response to visuomotor or forcefield perturbations.

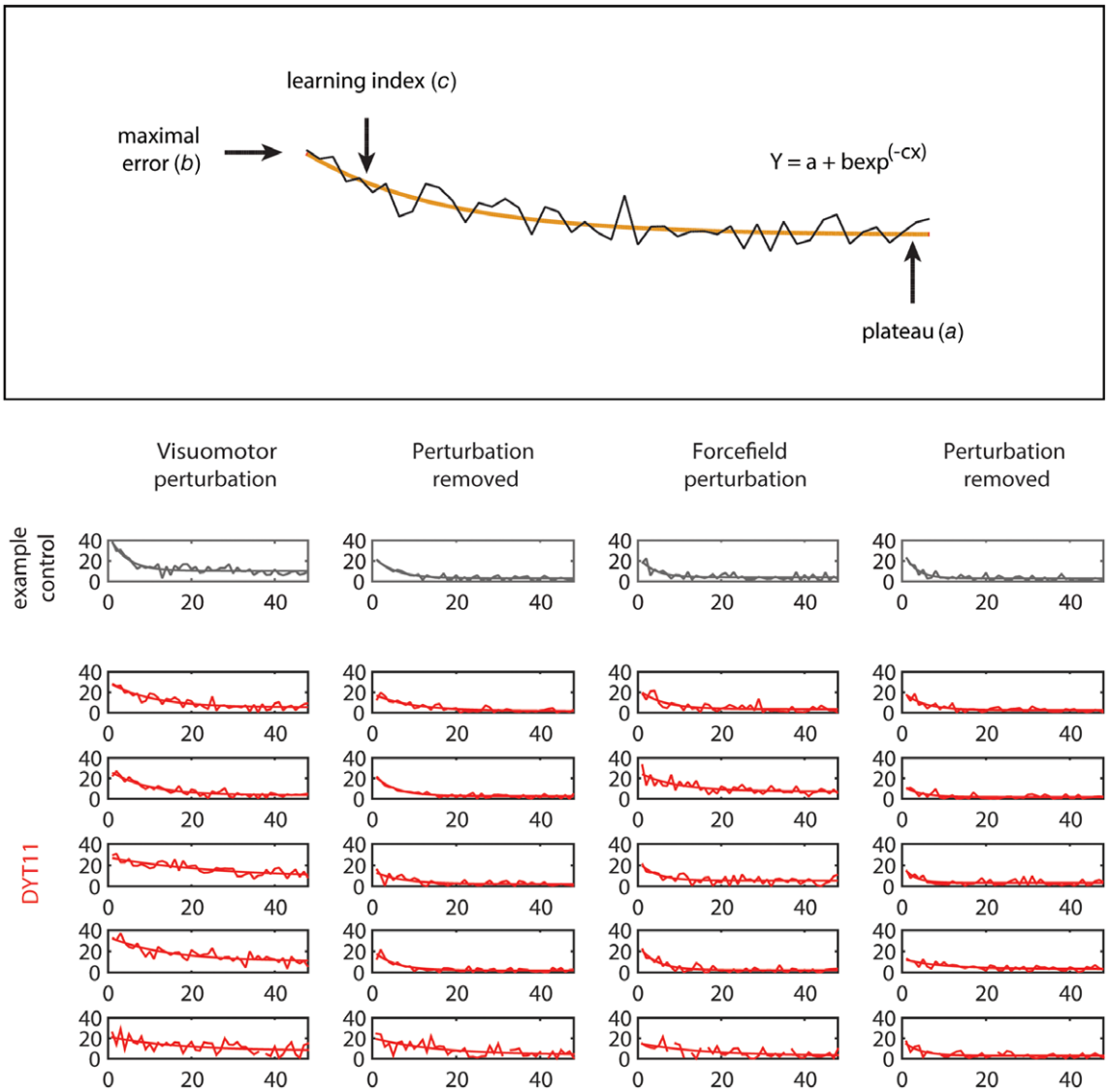

FIG. 2. Modeling adaptation revealed no significant deficit in any individual with DYT11. (A) Each of the 4 experimental conditions were modeled with an exponential function in which *Y* represents the predicted angular error, *a* is an estimate of the plateau of the learning curve, *b* is an estimate of the maximal initial error (the *y*-intercept), *c* estimates the learning index for each condition, and *x* is the epoch. The learning index is the percentage reduction in error for each epoch and is a measure of rate of adaptation. (B) Data from an example control and all patients are shown for each experimental condition. Absolute angular error at maximal velocity is shown in degrees on the *y*-axis, and the number of trials is shown on the *x*-axis. Visually, all patients can be seen to adapt well to both types of perturbation, and the accompanying statistical comparisons are shown in Supplementary Table 2.

Discussion

This study has revealed that a previously documented deficit in saccadic adaptation in DYT11 does not have an obvious correlate in symptomatic body regions when 2 different types of limb adaptation are examined. We discuss these results and their implications for theories on the role of cerebellar dysfunction in DYT11.

The cerebellum has received increasing interest in the study of movement disorders and a case has been made across animal and human studies for a cerebellar role in the pathophysiology of subtypes of myoclonus and dystonia, the core movement disorders exhibited in DYT11.[16,17] In addition, the partial alleviation of symptoms of DYT11 with alcohol, to which the cerebellum is highly sensitive, is often taken as a clinical marker of potential cerebellar involvement.[8,17] The causative mutation of DYT11 dystonia, ϵ-sarcoglycan, is expressed in multiple nonneural and neural regions throughout development.[18] Importantly, brain-specific isoforms demonstrate high expression in the Purkinje cells and neurones of the dentate nucleus,[8] and selective deficits in motor learning on a beam-walking test have been observed in a Purkinje cell-specific conditional knockout for ϵ-sarcoglycan.[6] In humans with DYT11 dystonia, imaging studies have revealed metabolic changes in the cerebellum (in conjunction with other regional abnormalities)[7] and impaired saccadic adaptation has been taken as

one of the first functional markers of cerebellar dysfunction in the disease.[9] Results with another associative cerebellar learning paradigm, eye blink conditioning, have to date been mixed (one study showing normal acquisition,[4] the other impaired acquisition)[17]. Whether the subclinical deficit in saccadic adaption was indicative of a more general deficit in adaptation was the core experimental question explored in this paper. Finding deficiencies in a cerebellum-dependent task in symptomatic limbs would take us closer to causally linking cerebellar dysfunction to the clinical movement disorder.

Interestingly, our data testing adaptation to visuomotor and forcefield perturbations in the symptomatic limbs of patients with DYT11 did not reveal a group deficit in adaptation to match the saccadic adaptation result previously found. Saccadic adaptation metrics were highly sensitive and highly specific for DYT11. Our sample size calculation based on these data and its variance show that our sample size was more than adequate for equivalent deficits in limb adaptation. In addition, individual participant data clearly demonstrate both an effective rate and magnitude of adaptation in all DYT11 patients in response to both perturbations (Fig. 2). These results, cannot rule out that a more subtle deficit in limb adaptation with a smaller effect size exists, simply that the large impairment observed in saccadic adaptation is not observed in limb adaptation.

How does one explain the discordance between impaired saccadic adaptation and intact limb adaptation? If both findings are valid, there are a number of potential explanations. First, there is some evidence that different cerebellar regions contribute to saccadic versus limb adaptation.[19] However, one would have to explain why a genetic defect in a protein, which is widely distributed in the cerebellum, would only cause a focal deficit.[20] Alternatively, the sensitivity of the tasks to detect cerebellar dysfunction may be different. For example, both limb adaptation tasks involved a consciously perceived abrupt visuo-spatial or proprioceptive error and therefore both implicit and explicit strategies are likely to be used.[21,22] Saccadic adaptation by contrast is a largely implicit task.[10] The neural correlates of such task-related differences are complex, but the cerebellum may be preferentially recruited with implicit paradigms that could therefore be important in driving the differences observed in DYT11.[23,24] Another alternative is that the saccadic adaptation deficits identify a cerebellar-independent mechanism that is revealed selectively by testing saccadic adaptation.[10] Saccadic and limb adaptation are likely to involve overlapping distributed networks, but certain features such as brain stem processing are clearly more important in the control of eye movements.[10]

There are few neurophysiological markers that have the power to segregate disease groups so cleanly as saccadic adaptation in DYT11. If the sensitivity and specificity of the impairment is confirmed it could be used as a screening tool to guide genetic analysis. In addition, better delineation of the exact features of the saccadic response that account for the deficit may correlate with disease severity potentially to objectively monitor therapeutic responses. To date saccadic adaptation in DYT11 has only been studied using an eye-brain machine in which the experimental paradigm is relatively fixed and the data analysis is automated. Reproducing the effect in DYT11 dystonia and determining the specificity of the finding within other myoclonus-dystonia subtypes is one interesting line of research. Experimenting with different types of adaptation and the influence the neuropsychiatric profile associated with DYT11 dystonia would also be informative. Saccadic adaptation is complex with performance dependent on many variables including cognitive influences such as the context of the paradigm and attentional factors.[10]

In summary, our study has shown healthy levels of adaptation (rate and magnitude) to visuomotor and forcefield perturbations in the symptomatic limbs of patients with DYT11. Therefore, the large impairment in saccadic adaptation observed in a previous study does not translate into a similarly large deficit in limb adaptation. If future studies confirm the sensitivity and specificity of the saccadic adaptation deficit, we suggest a hypothesis to be investigated that will better delineate the cerebellar role in DYT11 dystonia. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.