

## Delineating cerebellar mechanisms in DYT11 myoclonus-dystonia

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## **(1) Title Page**

**Title:** Delineating cerebellar mechanisms in DYT11 dystonia

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## **(2) Abstract**

**Background:** Recent research has highlighted the role of the cerebellum in the pathophysiology of myoclonus-dystonia syndrome due to mutations in the *ε-sarcoglycan* gene (DYT11). Specifically, a cerebellar-dependent saccadic adaptation task is dramatically impaired in this patient group.

**Objectives.** To investigate whether saccadic deficits co-exist 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 was examined in five patients with DYT11 and ten aged-matched controls.

**Results.** Patients with DYT11 successfully adapted to both types of perturbation. Modelled and averaged summary metrics which captured adaptation behaviour were equivalent to the control group across conditions.

**Conclusions.** DYT11 is not characterised by a uniform deficit in adaptation as 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 which need future study.

### (3) Introduction

Myoclonus-dystonia syndrome is a rare movement disorder with lightning-like myoclonic jerks, mild to moderate dystonia and associated psychiatric abnormalities<sup>1</sup>. The most frequent genetic cause of myoclonus-dystonia, DYT11, is due to loss of function mutations in the *ε-sarcoglycan* gene and is inherited in an autosomal dominant manner with incomplete penetrance<sup>2,3</sup>. With no overt neurodegeneration the disease is thought to represent a functional neural disturbance across a predominantly subcortical network<sup>4,5</sup>. 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<sup>6-8</sup>.

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<sup>9</sup>. 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<sup>10</sup>. 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<sup>9</sup>.

In this study, we investigated whether the observed deficit in saccadic adaptation co-exists 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 two 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<sup>11</sup>. 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<sup>12</sup>.

#### (4) Methods

Five patients with genetically proven DYT11 myoclonus dystonia were recruited from the National Hospital for Neurology and Neurosurgery (clinical details given in supplementary table) and data compared to ten aged matched controls (previously published<sup>13</sup>). 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 non-normality is also assumed an increase of subject numbers of 16% is generally advised giving a requirement for 3.70 or four individuals in each group<sup>14</sup>. The group of 10 controls further increased the reliability of our findings<sup>15</sup>. Therefore, we believe a patient group size of five 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 one of the four radially located targets through the control of a robotic manipulandum (Figure 1a). Each participant completed five experimental conditions in which baseline performance was assessed and then subjects were examined for their ability to adapt and washout both visuomotor and forcefield perturbations (Figure 1a). 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 (ii) 'error on removal' was estimated by calculating the mean error during the first eight trials once the perturbation had been removed.

In order to assess individual performance, we also modelled angular error using an exponential function for each for the four conditions (visuomotor adaptation learning and unlearning, forcefield adaptation learning and unlearning):

$$Y = a + b \exp(-cx)$$

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 analyse goodness of fit of the model.

Adaptation outcomes were compared by Mann-Whitney U test due to small sample size and the  $U$  statistic,  $p$  value and effect size ( $r$ ) are written for each comparison. A Bonferroni correction was applied when three model parameters were evaluated ( $0.05/3=0.016$ ). SPSS (IBM SPSS Statistics, v24) and Matlab (R2017a) were used for data analysis.

## **(5) Results**

During the baseline block, both groups made comparable and adequate reaches with no significant difference seen between groups for reaction time (control median 446.9ms, DYT11 median 466.6ms,  $U=22$ ,  $p=.71$ ,  $r=0.09$ ), movement time (control median 288ms, DYT11 median 314ms,  $U=24$ ,  $p=.90$ ,  $r=0.03$ ) 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 (Figure 1b). For the visuomotor perturbation, both late adaptation (Figure 1c,  $U=14$ ,  $p=.18$ ,  $r=.35$ ) and the initial error once the perturbation had been removed (Figure 1d,  $U=19$ ,  $p=.46$ ,  $r=.19$ ) were equivalent. Late adaptation (Figure 1e,  $U=18$ ,  $p=.44$ ,  $r=.22$ ) and initial error (Figure 1f,  $U=20$ ,  $p=.59$ ,  $r=.16$ ) were also equivalent for the forcefield perturbation.

In addition, we modelled adaptation data for each experimental condition. All individuals met the requirement that  $R^2$  was greater than 0.4 (i.e. model explained more than 40% of variation, no exclusions). The three parameters which described the fitted function (plateau, maximal error, learning rate) were also found to be equivalent across groups (Figure 2, statistics shown in Table 2 of 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.

## (6) 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 two 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<sup>16,17</sup>. 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<sup>8,17</sup>. The causative mutation of DYT11 dystonia, *ε-sarcoglycan*, is expressed in multiple non-neural and neural regions throughout development<sup>18</sup>. Importantly, brain specific isoforms demonstrates high expression in the Purkinje cells and neurones of the dentate nucleus<sup>8</sup> and selective deficits in motor learning on a beam walking test have been observed in a Purkinje cell-specific conditional knockout for *ε-sarcoglycan*<sup>6</sup>. In humans with DYT11 dystonia, imaging studies have revealed metabolic changes in the cerebellum (in conjunction with other regional abnormalities)<sup>7</sup> and impaired saccadic adaptation has been taken as one of the first functional markers of cerebellar dysfunction in the disease<sup>9</sup>. Results with another associative cerebellar learning paradigm, eye blink conditioning have to date been mixed (one study showing normal acquisition<sup>4</sup>, the other impaired acquisition<sup>17</sup>). Whether the subclinical deficit in saccadic adaptation 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.

Interesting, 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 sensitivity and highly specific for DYT11. Our sample size calculation based on this data and its variance show that that our sample size was more than adequate for equivalent deficits in limb adaptation. In addition, individual subject data clearly demonstrate both an effective rate and magnitude of adaptation in all DYT11 patients in response to both perturbations (Figure 2). However, these results cannot provide conclusive evidence that DYT11 patients do not suffer from more subtle deficits in limb adaptation

with smaller effect sizes, simply that the large impairment (and corresponding effect size) 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. Firstly, there is some evidence that different cerebellar regions contribute to saccadic versus limb adaptation<sup>19</sup>. 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<sup>20</sup>. 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<sup>21,22</sup>. Saccadic adaptation by contrast is a largely implicit task<sup>10</sup>. The neural correlates of such task-related differences are complex but the cerebellum may be preferentially recruited with implicit paradigms which could therefore be important in driving the differences observed in DYT11<sup>23,24</sup>. Another alternative is that the saccadic adaptation deficits identify a cerebellar independent mechanism which is revealed selectively by testing saccadic adaptation<sup>10</sup>. Saccadic and limb adaptation are likely to involve overlapping distributed networks but certain features such as brainstem processing are clearly more important in the control of eye movements<sup>10</sup>.

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 which account for the deficit may correlate with disease severity potentially in order 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<sup>10</sup>.

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 hypothesis to be investigated which will better delineate the cerebellar role in DYT11 dystonia.

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### **(8) Authors' Roles**

AS 1A, B, C 2A, B 3A

JMG 1A, B, C, 2C, 3B

JC 1 C, 2C, 3B,

TTW 1A, 2C, 3B

KPB 1A, 2C, 3B

JCR 1A, 2C, 3B

MJE 1A, 2C, 3B

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JCR has received speaker travel costs from the Movement Disorders Society.

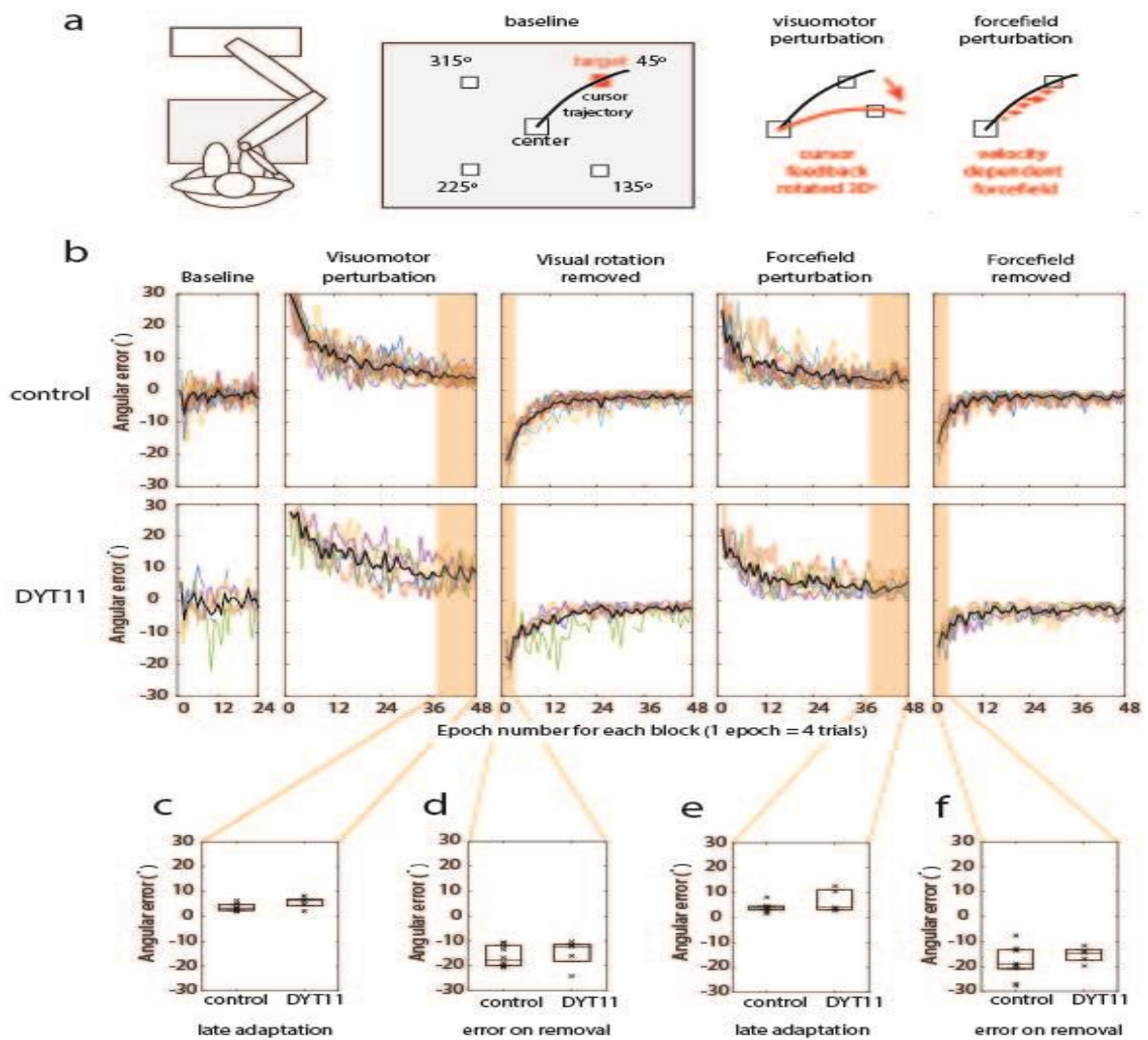
MJE: receives royalties from publication of *Oxford Specialist Handbook Of Parkinson's Disease and Other Movement Disorders* (Oxford University Press, 2008) and receives research support from a National Institute for Health Research (NIHR) grant where he is the principle investigator. He has received honoraria for speaking from UCB.

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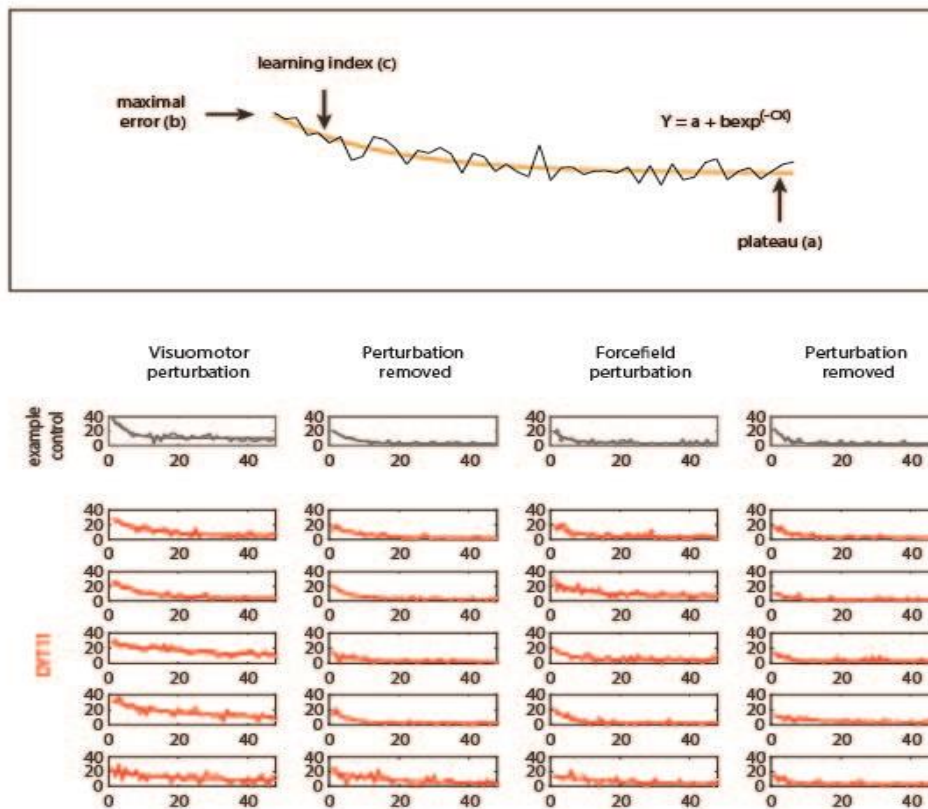
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**Figure 1 Patients with DYT11 adapt healthily to both visuomotor and forcefield perturbations. 1a** | Experimental setup and illustration of the two types of adaptation tested. In the visuomotor condition visual feedback was distorted by 30° in the 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)). **1b** | Individuals' adaptation behaviour is indicated by coloured lines and the group mean is shown by a thicker black line. At both the individual and group level DYT11 patients adapted to both types of perturbation (gradually reducing angular error as the perturbation is on-going). When the perturbation is removed error in the opposite direction is seen and the perturbation is gradually unlearned. **1c** | In order to facilitate comparison to previous papers we quantified mean adaptation at two time points; the last 40 trials of the perturbation ('late adaptation') and the first eight 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 the error on removal of both perturbations were equivalent.



**Figure 2 Modelling adaptation revealed no significant deficit in any individual with DYT11. 1a |** Each of the four experimental conditions were modelled 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. **1b |** 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.

**Table 1: Clinical characteristics of patients.** Subjects did not have any additional neurological or musculoskeletal problems of the arm or significant cognitive impairment. Myoclonus severity was assessed using the Unified Myoclonus Rating Scale (UMRS) which is composed of eight components: autoevaluation (AE), presence of rest myoclonus (rest), stimulus sensitivity (stim sens), presence of action myoclonus (act), function impairment (func), global disability score (GDS), negative myoclonus score (neg), negative myoclonus severity score (neg sev)<sup>6</sup>. Severity of dystonia was assessed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFM)<sup>7</sup>. There was no significant difference between groups for age  $t(14)=-0.30, p=0.76$ . Mean and standard deviation (std) are given.

<b>DYT11</b>												
	<b>Age</b>	<b>Sex</b>	<b>Medications</b>	<b>UMRS</b>							<b>BFM</b>	
				AE	rest	Stim sens	Action	func	GDS	neg		neg sev
	60	F	Propranolol 20 mg od, Diazepam 5 mg bd	13	8	4	28	9	2	1	2	2.5
	21	F	Levetiracetam 250 mg bd	12	1	0	0	2	1	0	0	2
	50	F	Gabapentine 300 mg od	22	14	5	35	10	2	0	0	10
	38	M	Clonazepam 500 mcg tds	28	36	9	62	15	2	1	2	4
	46	F	Clomipramine for mild depression	23	5	3	20	11	3	1	1	10
<b>Mean (std)</b>	<b>43 (14.6) years</b>											
<b>Control</b>												
<b>Mean (std)</b>	<b>45.5 (15.4) years</b>											

**Table 2: Modelling adaptation and unlearning revealed no significant deficit in DYT11.**

Group median for each parameter plateau (a), maximal error (b), and learning index (c) for each experimental condition with accompanying Mann-Whitney group comparison. Three comparisons set the significance level at  $p=0.016$  (Bonferonni correction:  $0.05/3 = 0.016$ ).

	controls	DYT11	Mann-Whitney U
visuomotor adaptation			
plateau (a)	4.26	7.69	$U=11.0, p=.086, r=.44$
maximal error (b)	28.9	23.2	$U=8.0, p=.037, r=.54$
learning index (c)	0.825	0.681	$U=12.0, p=.111, r=.41$
perturbation removed			
plateau (a)	2.10	2.29	$U=20.0, p=.540, r=.16$
maximal error (b)	24.0	16.8	$U=6.0, p=.020, r=.60$
learning index (c)	0.200	0.150	$U=14.0, p=.178, r=.35$

	controls	DYT11	Mann-Whitney U
forcefield adaptation			
plateau (a)	3.13	3.44	$U=16.0, p=.270, r=.28$
maximal error (b)	21.0	18.8	$U=18.0, p=.391, r=.22$
learning index (c)	0.174	0.174	$U=25.0, p=1.0, r=.0$
perturbation removed			
plateau (a)	1.97	2.88	$U=12.0, p=.111, r=.29$
maximal error (b)	21.1	15.0	$U=10.0, p=.066, r=.47$
learning index (c)	0.345	0.253	$U=10.0, p=.066, r=.47$



## Supplementary Methods

Participants were seated with their forehead supported on a headrest and their semipronated right hand gripped a manipulandum underneath a horizontally suspended mirror (Figure 1a). The mirror prevented direct vision of the hand and arm and showed a reflection of a computer monitor mounted above. The visual display comprised of a central 30 mm square indicating starting position, a 5 mm diameter circular cursor representing the position of the manipulandum and a 10mm square target at one of four radially arranged positions 90 mm from the center (45°, 135°, 225° or 315°). The start of the trial was indicated by the appearance of the target and subjects were instructed to 'shoot' through the target with a smooth arm movement. The cursor was visible throughout the trial. If movement duration was greater than 300ms the target changed from white to blue at the end of the trial indicating that the movement was too slow. After completion of the outward movement participants were asked to relax and allow the robotic arm to return the arm to the central starting position. Once the cursor was re-centered the next target would appear. Participants familiarised themselves with the basic task by performing 25 trials during in which verbal feedback was given to further explain the desired movement (data not analysed).

Each participant then completed five experimental conditions in which baseline performance was assessed and then subjects were examined for their ability to adapt and washout both visuomotor and forcefield perturbations (Figure 1a). 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)). The type of adaptation perturbation was counterbalanced such that if the first perturbation was positive visuomotor the second perturbation was negative forcefield (giving four possible order combinations).

Hand rate was sample at a rate of 200Hz. The start time ( $t_1$ ) of movement was defined as the time point at which 10% of maximal velocity of that trial was reached. The end of movement was defined as the time at which the target perimeter was first breached by subject movmenet ( $t_2$ ). Movement duration was the difference between these two values ( $t_2-t_1$ ). Reaction time was calculated as the difference between the time of target presentation ( $t_0$ ) and the start of movement ( $t_1-t_0$ ). Angular error was the angle in degrees from target direction at maximal velocity. Trials that had an angular error >45°, a movement duration of <200ms or >800ms, or a reaction time <200ms or >600ms were excluded. Epochs were created by taking an average value across four consecutive trials. The study was approved by the local ethics committee and was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.