Impaired body movement representation in *DYT1* mutation carriers ☆

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Abstract

Objective: The only known genetic cause of early-onset primary torsion dystonia is the GAG deletion in the DYT1 gene. Due to the reduced penetrance, many mutation carriers remain clinically asymptomatic, despite the presence of subclinical abnormalities, mainly in the motor control circuitry. Our aim was to investigate whether the DYT1 mutation impairs the inner simulation of movements, a fundamental function for motor planning and execution, which relies upon cortical and subcortical systems, dysfunctional in dystonia.
Methods: DYT1 manifesting patients, DYT1 non-manifesting carriers and control subjects were asked to fixate body (hand, foot, face) or non-body (car) stimuli on a computer screen. Stimuli were presented at different degrees of orientations and subjects had to mentally rotate them, in order to give a laterality judgement. Reaction times and accuracy were collected.
Results: DYT1 carriers, manifesting and non-manifesting dystonic symptoms, were slower in mentally rotating body parts (but not cars) than control subjects.
Conclusions: The DYT1 gene mutation is associated with a slowness in mental simulation of movements, independently from the presence of motor symptoms.
Significance: These findings suggest that the cognitive representation of body movements may be altered subclinically in dystonia, thus contributing to the endophenotypic trait of disease.
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Keywords: DYT1 gene; Dystonia; Mental rotation; Movement representation; Endophenotype

1. Introduction

DYT1 primary torsion dystonia is characterized by prolonged muscular contractions causing abnormal torsion movements and sustained postures (Bressman, 1998; Albanese et al., 2006). This movement disorder is due to a 3bp GAG deletion in the TOR1A gene, which manifests in only 20–40% mutation carriers (Ozelius et al., 1997). The mechanisms underlying reduced penetrance are poorly understood, although three DYT1 polymorphisms have been recently shown to influence penetrance (Risch et al., 2007). Subclinical abnormalities in manifesting and non-manifesting DYT1 carriers have been demonstrated, suggesting that some alterations might be regarded as endophenotypic traits of the DTY1 mutation (Eidelberg et al., 1998; Trost et al., 2002; Edwards et al., 2003; Ghilardi et al., 2003; Carbon et al., 2004; Fiorio et al., 2007a). Indeed, DYT1 carriers show an abnormal pattern of

glucose utilization characterized by hypermetabolism in the supplementary motor area, the basal ganglia and the cerebellum (Eidelberg et al., 1998; Trost et al., 2002; Carbon et al., 2004). Of note, the neural pathways interconnecting these areas are relevant to different stages of motor control. One fundamental mechanism underlying motor control is the ability to predict the correct sequence of movements to be executed and the final position of the body part. A useful tool to investigate movement prediction is the mental rotation paradigm, based on the ability to imagine a body part or an object in a different perspective from the one in which it actually appears. This process requires an inner simulation of real perceptual and motor performance and, when regarding body parts, it is carried out by simulating actual body movements (Parsons, 1994). Cortical and subcortical networks probably underlying mental rotation of body parts and objects include posterior parietal and occipital cortices, motor, premotor and supplementary motor areas, basal ganglia and cerebellum (Bonda et al., 1995; Parsons et al., 1995; Kosslyn et al., 1998; Ganis et al., 2000; Sirigu and Duhamel, 2001; Vingerhoets et al., 2002; Wolbers et al., 2003; de Lange et al., 2005).

Interestingly, patients with primary non-DYT1, late-onset focal-hand and cervical dystonia showed impaired mental rotation of body parts either affected or unaffected by dystonia (Fiorio et al., 2006, 2007b), raising the possibility that altered performance represents an endophenotypic trait of primary dystonia.

In this paper, we studied whether mental rotation of body parts was impaired in DYT1 carriers, both manifesting and non-manifesting dystonic symptoms, as compared to normal subjects.

2. Methods

2.1. Subjects

DYT1 dystonia patients and DYT1 unaffected carrier relatives (7 first-degree, 2 second-degree and 3 third-degree relatives) were recruited among four Italian families. All participants have been carefully examined by a neurologist with the twofold aim of detecting the presence of dystonic symptoms and of evaluating the severity of disease. We were therefore able to separate the DYT1 carriers with dystonic signs (*DYT1 manifesting patients*) from their relatives without dystonia (*DYT1 non-manifesting relatives*). We included participants with (or corrected to) normal sight and without neurological disease (apart from dystonia in the patients' group).

2.1.1. DYT1 manifesting patients

Twelve patients (five women; mean age: 37.8 ± 15.2 years; mean education level: 9.1 ± 2.7 years; mean duration of disease: 18.8 ± 11.1 years) with primary torsion dystonia due to the GAG deletion in the DYT1 gene have been recruited. Table 1 shows patients' demographic and clinical information. The Burke–Fahn–Marsden movement and disability scale (Burke et al., 1985) have been used to evaluate the severity of motor impairment. Four patients (numbers 1, 3, 7, and 12) were untreated; three patients (numbers 2, 4, and 9) have been treated with botulinum toxin until 6 months before the study and five patients (numbers 5, 6, 8, 10, and 11) had a bilateral deep brain stimulator in the globus pallidus pars interna. Stimulators have been kept on during the experiment.

2.1.2. DYT1 non-manifesting relatives

Twelve healthy carriers of the DYT1 mutation (five women; mean age: 50.0 ± 20.9 years; mean education level: 9.3 ± 3.3 years) without dystonic clinical signs were recruited among patients' relatives.

2.1.3. Control subjects

Twelve healthy control subjects (eight women; mean age: 41.2 ± 18.3 years; mean education level: 10.8 ± 4.8 years) were also recruited.

A one-way ANOVA on age and education levels revealed no significant differences between these groups

Table 1
Information on the DYT1 manifesting patients

Gender	Age/education (years)	Age at onset (years)	Site of onset	Symptoms distribution	Motor impairment[a]	Treatment
F	26/11	10	L arm	Multi-focal	17	No
M	51/5	43	Neck	Generalised	22	BTX
M	29/8	22	R arm	Focal	2	No
F	70/8	43	Neck	Generalised	38.5	BTX
M	37/8	8	R leg	Generalised	65.5[b]	DBS
F	28/13	20	L arm	Focal	2[b]	DBS
F	48/13	39	L arm	Focal	6	No
M	27/13	8	R leg	Generalised	124[b]	DBS
F	38/8	9	L arm	Generalised	59	BTX
M	11/6	5	R arm	Generalised	4[b]	DBS
M	44/8	13	R leg	Generalised	24[b]	DBS
M	45/8	11	L leg	Generalised	8	No

R, right; L, left.
[a] Burke–Fahn–Marsden scale (Burke et al., 1985).
[b] Evaluation with stimulators on; BTX, botulinum toxin; DBS, deep brain stimulators.

(age: $p = 0.257$; education: $p = 0.464$). Written informed consent was collected for all subjects. Consent of subjects under 18 years old was given by the parents. The study was carried out in accordance with the ethical standards of the 1964 Declaration of Helsinki.

2.2. Stimuli and procedure

Two experiments, presented with counterbalanced order, were designed in order to test laterality judgements of body parts (hand, foot, head, Experiment 1) and non-corporeal object (car, Experiment 2). In Experiment 1, photos of hands, feet and heads (48 stimuli each) appeared on a computer screen. Hands and feet could be the left or the right ones. The head had a black patch positioned either on the left or on the right eye. Stimuli could appear in the upright position (0°) or rotated clockwise in 60°-steps (60°, 120°, 180°, 240°, 300°). Subjects had to report verbally the laterality of the presented stimuli (hand, foot, black-patched eye), by uttering 'left' or 'right' into a microphone. In Experiment 2, subjects saw the frontal view of a red car (48 stimuli) with the same degrees of orientation and had to report whether a black patch was on the left or right headlight. Images disappeared only after subjects' response. Reaction time (RT) was the time between stimulus onset and subjects' verbal response. Only RTs to trials with correct response were included in data analyses. Subjects' response type (left or right) was keyed into the computer by the experimenter. The percentage of correct responses on the total number of stimuli was used as an accuracy index.

2.3. Statistics

RTs and accuracy were analysed with separate repeated measures analyses of variance (ANOVAs). In Experiment 1, each ANOVA had the between-subjects factor "Group" (DYT1 manifesting patients, DYT1 non-manifesting relatives, control subjects) and three within-subjects factors, "Stimulus type" (hands, feet, head), "Stimulus side" (right, left) and "Stimulus orientation" (0°, 60°, 120°, 180°, 240°, 300°). Experiment 2 had "Group" as between-subjects factor and "Stimulus side" and "Stimulus orientation" as within-subjects factors. Two-tailed t-tests with Bonferroni's correction were used for post-hoc comparisons. Assessment of possible relationship between DYT1-dystonia severity score (Burke et al., 1985) and performance was made by means of the Spearman correlation coefficient. P values ⩽0.050 were statistically significant.

3. Results

3.1. Laterality judgements of body parts

3.1.1. Reaction times

The Group was significant ($F(2, 33) = 4.7$; $P = .015$) in that RTs were faster in controls (mean ± SD, 1076.4 ms ±

136) than in DYT1 carriers, manifesting (1592.1 ms ± 262.1) and non-manifesting (1592.6 ms ± 179.4). The significance of Stimulus side ($F(1, 33) = 22.1$; $P < .001$) was due to subjects' faster RTs in rotating right (1355.8 ms ± 288.7) than left stimuli (1484.9 ms ± 328). Stimulus orientation was also significant ($F(5, 165) = 12.1$; $P < .001$), insofar as RTs were longer at 180° (1653.4 ms ± 361.8) than at 0° (1371.4 ms ± 304.1), 60° (1329.1 ms ± 266.6), 120° (1409.9 ms ± 248), 300° (1296.5 ms ± 241.9). Significant post-hoc comparisons for the interaction Stimulus type × Stimulus side × Stimulus orientation ($F(10, 330) = 2.2$; $P = .018$) are summarised in Table 2. The lack of significance in the Group × Stimulus Type interaction suggests that the longer RTs observed in DYT carriers with respect to controls were comparable for the hand, foot and head stimuli (Fig. 1a).

3.1.2. Accuracy

The Group did not reach significance ($P = .174$). Stimulus type was significant ($F(2, 66) = 3.9$; $P = .024$), insofar as participants were less accurate in rotating feet (mean ± SD, 79.4% ± 7.9) than heads (84.9% ± 8.3). Stimulus orientation was also significant ($F(5, 165) = 13.1$; $P < .001$), due to the lower accuracy for stimuli oriented at 180° (74.9% ± 8.4) than at 0° (84% ± 4.1), 60° (86.2% ± 6.2), 120° (80.9% ± 6.5), 240° (81.5% ± 9), 300° (87% ± 6.2). Post-hoc comparisons on the interaction Stimulus type × Stimulus side × Stimulus orientation ($F(10, 330) = 2.0$; $P = .034$) are shown in Table 3.

Neither RTs nor accuracy in laterality judgements of hands, feet or heads was correlated with dystonia severity scores ($r < .532$, $P > .075$).

3.2. Laterality judgements of non-body object

3.2.1. Reaction time

The Group was not significant ($P = .106$). Stimulus side was significant ($F(1, 33) = 7.3$; $P = .011$), being right stim-

Table 2
Significant post-hoc comparisons in reaction times (RT)

RT	Right-side stimuli			Left-side stimuli		
	Degree(ms) vs.	Degree(ms)	P	Degree(ms) vs.	Degree(ms)	P
Hand	0°(1314)	180°(1640)	.003	0°(1408)	180°(1645)	.009
	60°(1309)	180°(1640)	<.001	60°(1304)	180°(1645)	.007
	180°(1640)	240°(1325)	.007	60°(1304)	240°(1753)	.008
	180°(1640)	300°(1187)	<.001	120°(1369)	180°(1645)	.001
				120°(1369)	240°(1753)	.008
Foot	0°(1233)	180°(1559)	.002	0°(1404)	180°(1758)	<.001
	0°(1233)	240°(1478)	.005	60°(1445)	180°(1758)	.001
	60°(1257)	180°(1559)	.001	120°(1472)	180°(1758)	<.001
	60°(1257)	240°(1478)	.009	180°(1758)	300°(1388)	<.001
	180°(1559)	300°(1258)	.003			
	240°(1478)	300°(1258)	.005			
Head	0°(1346)	300°(1178)	.002	60°(1401)	180°(1826)	.01

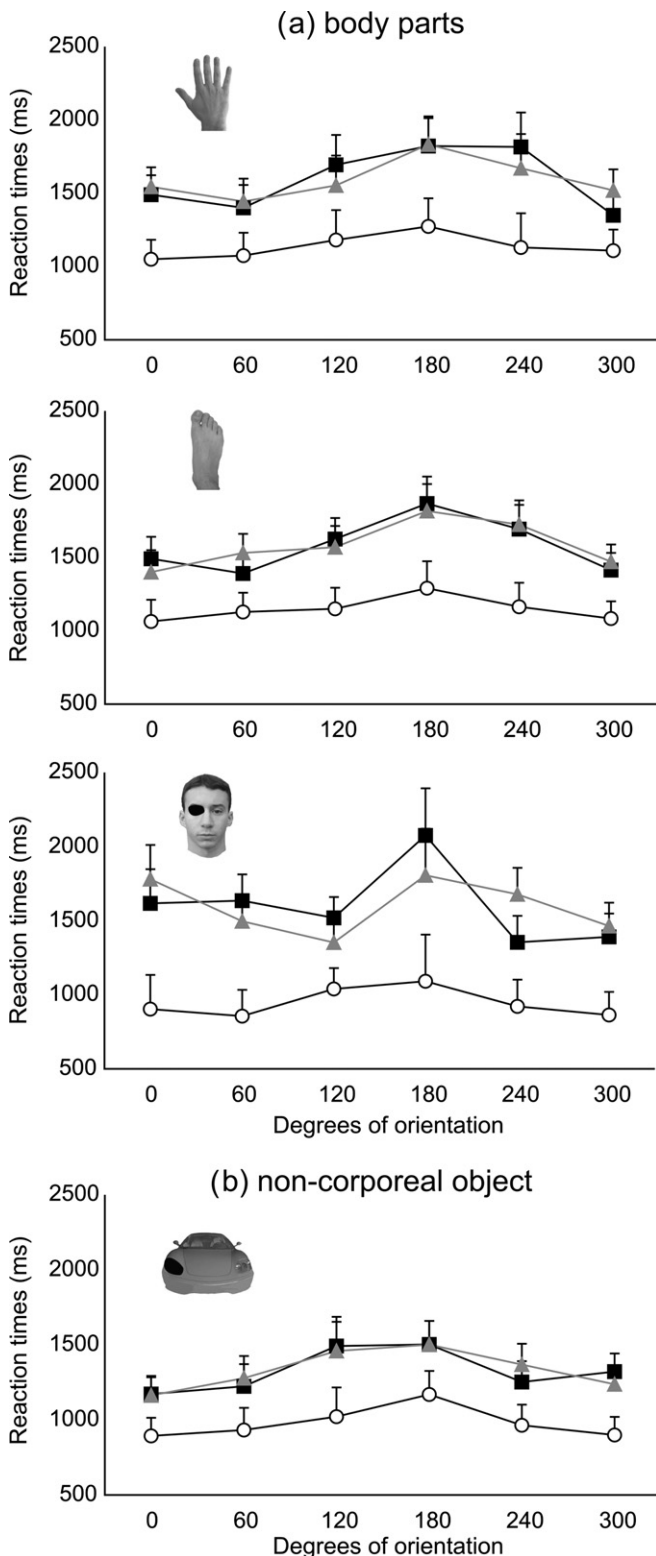## (a) body parts

(b) non-corporeal object

Fig. 1. Mean RTs and standard errors of the three groups (DYT1 manifesting, black squares; DYT1 non-manifesting, grey triangles; control subjects, white circles) in (a) mental rotation of body parts and (b) mental rotation of a non-corporeal object.

uli (1165.8 ms ± 216.9) faster to be rotated than left ones (1263.1 ms ± 218.6). Stimulus orientation was significant ($F(5, 165) = 7.2$; $P < .001$), due to longer reaction times at

Table 3
Significant post-hoc comparisons in accuracy (ACC)

ACC	Right-side stimuli			Left-side stimuli		
	Degree(%) vs.	Degree(%)	P	Degree(%) vs.	Degree(%)	P
Hand	120°(77)	300°(89)	.001	60°(90)	180°(76)	.003
	180°(77)	300°(89)	.009	180°(76)	300°(86)	.008
Foot	0°(84)	180°(67)	.003	0°(83)	240°(72)	.01
	60°(85)	180°(67)	<.001			
	180°(67)	240°(80)	.008			
	180°(67)	300°(85)	<.001			
Head	0°(86)	180°(75)	<.001	180°(76)	240°(88)	.006
	120°(86)	180°(75)	.01	180°(76)	300°(89)	.01
	180°(75)	300°(90)	.003			

180° (1391.2 ms ± 180.6) than at 0° (1076.8 ms ± 150.8), 60° (1145 ms ± 214.5), 120° (1324.8 ms ± 267.5), 240° (1195.7 ms ± 200.6), 300° (1153.1 ms ± 201.7) (Fig. 1b).

3.2.2. Accuracy

No effects or interactions were significant.

No correlation between patients' severity scores and RTs or accuracy was found ($r < .189$, $P > .556$).

4. Discussion

Despite showing similar accuracy in performing the task, patients with DYT1 dystonia and clinically unaffected carrier relatives were slower than control subjects in giving laterality judgements of body parts, such as hands, feet and heads. Since DYT1 carriers' ability to rotate a non-corporeal object was not significantly different from that of control subjects, we argue that impairment in body stimuli is not due to a general unspecific abnormality in mental rotation. It is still unclear whether or not mental rotation of objects and body parts shares common mechanisms (Kosslyn et al., 1998). Nevertheless, our observations raise the possibility that the mechanisms contributing to the two functions are, at least in part, different. In keeping with previous studies (Parsons, 1994), stimulus orientation implying stronger anatomical constraints in real movement execution, that is 180°, was the most difficult to rotate (with the lowest accuracy and the longer RTs) for all stimuli and both sides. This would suggest that mental rotation in our subjects was performed by mentally simulating actual movements.

The ability to mentally rotate body parts relies on a neural network implicated in the integration of sensory information with motor actions. Cortical motor and premotor areas, parietal and occipital areas, and the basal ganglia probably contribute to this network (Kosslyn et al., 1998; Vingerhoets et al., 2002; Wolbers et al., 2003; de Lange et al., 2005). As recently suggested, parietal and occipital cortices seem to be firstly involved in mental rotation, while motor areas might be involved in rotation by processing anatomical biomechanical constraints, or by checking the final imagined body position (Thayer and Johnson,

2006). Connectivity, a process by which the activity of different brain regions is dynamically integrated, is also important for mental rotation efficiency. In an electrophysiological study, mental rotation aptitude was related to increased frontal–parietal functional connectivity (Silberstein et al., 2003). The reduced ability to correctly execute the mental rotation task might therefore result from abnormalities at various levels of this network.

Although the mechanisms underlying mental rotation deficits showed by DYT1 carriers remain to be fully determined, a few points can nevertheless be made. Both manifesting and non-manifesting DYT1 carriers are characterized by impaired sensory discrimination of tactile stimuli (but not of visual stimuli, which are only present in manifesting carriers) (Fiorio et al., 2007a), by glucose hypermetabolism in the supplementary motor area, basal ganglia, and cerebellum (Eidelberg et al., 1998; Trost et al., 2002), and by increased activation in the left premotor cortex and right supplementary motor area and reduced activity in the posterior medial cerebellum during motor execution (Ghilardi et al., 2003). Finally, DYT1 carriers and idiopathic dystonia patients show abnormal anatomical connectivity in the sensorimotor cortex, namely reduced axonal integrity and coherence (Carbon et al., 2004, 2008 Bonilha et al.,2007). Taken together, all these observations suggest that the impairment of mental rotation observed in the current study may be the consequence of a dysfunction in the circuitry underlying motor control mechanisms and somatosensory information processing, and/or in functional/anatomical connectivity.

Mental rotation of body parts is performed by simulating one's own actual body movements (Parsons, 1994). This covert action simulates real movement execution, thus allowing to disentangle the laterality of a presented body part. A motor simulation mechanism is operating even when we observe actions performed by other individuals (Fadiga et al., 1995). The simulation theory assumes that this mechanism grounds the process of action understanding, by matching observed actions onto their inner motor representation (Gallese and Goldman, 1998; Rizzolatti and Craighero, 2004). It has been suggested that the handedness discrimination task might engage the mirror neuron system (Gawryszewski et al., 2007). Although similar, however, the two mechanisms of motor simulation do not seem to completely overlap, thus allowing a differentiation between oneself and another agent (Jeannerod, 2007).

Mental rotation abnormalities characterized by slow reaction times have been recently reported in primary adult-onset dystonia (Fiorio et al.,2006, 2007b), a condition that is not usually associated to the DYT1 gene mutation. This observation raises doubt on the specificity of the current findings in the DYT1 setting. However, recent data have shown a possible role of DYT1 polymorphic variants as risk factors to develop sporadic primary late-onset dystonia (Clarimon et al., 2005; Kamm et al., 2006).

The abnormal mental rotation of body parts found in both manifesting and non-manifesting DYT1 carriers is consistent with a subclinical alteration of the cognitive representation of body movements in dystonia. Whether this alteration is due to altered sensory processing, to defective motor circuit, or to impaired functional/anatomical connectivity, remains to be elucidated. Our findings add to the increasing evidence indicating the existence of subclinical alterations associated with the DYT1 mutation.

Whether this paradigm might help to disclose subclinical abnormalities in family members of dystonic patients, facilitating the detection of potential novel gene mutations, needs further validation on a larger sample of gene carriers and control subjects, as well as application on patients with diagnosis of a non-dystonic disorder.

Conflict of interest

We declare no conflicts of interest.

Acknowledgements

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