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# 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.


*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

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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: $37.8 \pm 15.2$ years; mean education level: $9.1 \pm 2.7$ years; mean duration of disease: $18.8 \pm 11.1$ 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: $50.0 \pm 20.9$ years; mean education level: $9.3 \pm 3.3$ years) without dystonic clinical signs were recruited among patients' relatives.

#### 2.1.3. Control subjects

Twelve healthy control subjects (eight women; mean age: $41.2 \pm 18.3$ years; mean education level: $10.8 \pm 4.8$ 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.