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Developmental lag of visuospatial attention in Duchenne muscular dystrophy

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ABSTRACT

Children with Duchenne muscular dystrophy (DMD) present a specific deficit of voluntary attention but to date there has been no clear characterization of their attentional skills. The present study investigated the hypothesis that DMD patients present deficits of both voluntary and automatic visuospatial attention systems and that their performance could be equivalent to that of younger healthy males. Twenty males (mean age 10 years) with diagnosis of DMD, 20 age-matched healthy males (10 years 3 months) and 20 healthy younger males (7 years 6 months) were required to perform two visuospatial attention tasks: voluntary and automatic. In the voluntary task, the performance of the DMD group was significantly worse than that of the age-matched group, and equal to that of the younger controls. In the automatic attention task also, the performance of the DMD patients was less efficient than that of the age-matched controls and equal to that of the younger children. This study supports the previous report of voluntary attention deficit in DMD and extends the evidence to include also an automatic attention system deficit. The development level of attention in DMD patients is below that expected for their age and corresponds to a delay of about three years.

1. Introduction

Duchenne muscular dystrophy (DMD) is a neuromuscular disease which has a major impact on the lives of the affected individuals, their families, and society. This genetic pathology affects one in every 5000 newborn males and is inherited in an X-linked recessive pattern (Blake & Kröger, 2000; Mehler, 2000; Miller & Wessel, 1993). The mutation process of the Xp21 (or DMD) gene, which encodes a protein called dystrophin, produces muscle weakness and physical limitations associated with cognitive and neuropsychological deficits (Wicksell, Kihlgren, Melin & Eeg-Oloffson, 2004). The latter are not progressive, unlike the muscular symptoms.

Dystrophin is found mainly in the muscle fibers, but occurs also in other organs such as the brain and the retina. This protein is expressed during several specific isoforms, some exclusive, others predominant in the brain (Lidov, 2000).

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Ricotti, Roberts, and Muntoni (2011) suggested that dystrophin plays a role in GABAergic synapses, critical in cognitive functions. Consequently, cognitive assessments carried out in DMD individuals showed impairment in executive functions, attention and verbal memory (Cotton, Voudouris & Greenwood, 2000; Marini et al., 2007; Mento, Tarantino & Bisiacchi, 2011; Poysky, 2007). Several studies in the last decades confirmed that individuals affected by DMD may present compromised cognitive development. The Intellectual Quotient (IQ) of Duchenne patients is normally one standard deviation below the average for the general population (Cotton et al., 2000). Moreover, the result of genotype-phenotype correlation in DMD showed that individuals with mutations affecting all the isoforms (downstream of exon 63) usually presented an intellectual disability. Conversely, individuals with mutations affecting only full-length isoforms (upstream of exon 30) less frequently presented intellectual disability (Ricotti et al., 2011).

Recently, higher rates (11–33%) of comorbid disorders, including attention-deficit-hyperactivity (ADHD), have been reported in Duchenne patients (Hendriksen & Vles, 2008; Pane et al., 2012; Steele et al., 2008). Despite growing interest in this comorbidity, few systematic studies have been carried out. Most of these investigations used parental questionnaires or surveys in their methodology, while in other studies attention deficit was evidenced using neuropsychological tasks (Cotton, Crowe & Voudouris, 1998; Hinton, De Vivo & Nereo, 2000). However, the presence of attention impairment in DMD is still controversial owing to the small number of studies, some of which excluded attention dysfunction (Hinton et al., 2000; Mento et al., 2011).

Dystrophin is concentrated in the postsynaptic pyramidal cells of the cerebral cortex (especially in the deep layers of the frontal cortex), in the hippocampus and in the soma and dendrites of Purkinje cells in the cerebellum. Therefore, dystrophin is mainly expressed in the frontal networks involved in attention orienting. In fact, fMRI studies in healthy individuals showed that a dorsal fronto-parietal network is active during top-down attention control, which is voluntary driven by semantic information (endogenous stimulus). A second network, made up of ventral fronto-temporo-parietal areas seems to be modulated by the detection of unexpected or peripheral events (exogenous stimuli) which automatically capture our attention (Corbetta & Shulman, 2002; Corbetta, Kincade, Ollinger, McAvoy & Shulman, 2000; Corbetta, 1998; Perry & Zeki, 2000).

The only study in which an experimental manipulation of attention has been carried out in patients with DMD is that of De Moura, Do Valle, Resende, and Pinto (2009). They used two Posner type tasks to evaluate voluntary and automatic visual orienting of attention with minimum working memory involvement. In the Posner paradigm, the participants respond to a target stimulus as quickly as possible. In the valid condition, the locus of target appearance is anticipated by a visual cue. In the invalid condition, however, the cue does not indicate the position of the target which will follow (Posner & Mitchell, 1967; Posner, 1980). In the automatic attention task, the cue is peripheral to the fixation point and automatically captures the attentional focus (exogenous stimulus). In the voluntary attention task, the cue appears in a central position and requires semantic processing (endogenous stimulus).

From the analysis of reaction times (RTs) obtained by De Moura et al. (2009) it emerged that patients with DMD present significantly increased attentional costs and benefits compared to the control group only in the voluntary attention task. DMD patients also showed a larger error rate in the invalid condition. Moreover, on the basis of previous studies on attentional control conducted in samples of children with typical development (Perchet & Garcia-Larrea, 2005; Wetzel & Schröger, 2007), De Moura and colleagues hypothesized that their 12-year-old DMD subjects would perform similarly to a group of 6–9-year-old children with typical development. However the authors did not directly verify this hypothesis.

De Moura et al. (2009) considered their results as evidence of voluntary, but not automatic, attention deficit in DMD. However, careful observation of the data reveals significantly longer reaction times (RTs) of DMD compared to controls (about 375 ms vs. 310 ms respectively) in the automatic orienting of attention task (valid condition). This result is therefore consistent with difficulties even in the automatic attention system.

The authors stated that longer raw RTs are just a sign of a motor deficit of the DMD group. However, similar mean RTs of the two groups (about 320 ms vs. 325 ms) were observed in the "valid condition" of the voluntary attention task, where the cue is effectively informative of the target position (less cognitively demanding condition). This result would indicate that the cognitive processing of the stimuli, more than the motor deficit, is responsible for the RT delay.

The main goal of this research is to investigate attentional skills in subjects impacted by the absence of full-length dystrophin expression, as occurs in DMD. In particular, we hypothesize that patients with DMD present deficits of both voluntary and automatic visuospatial attention orienting systems. Moreover, the present study aims to test the hypothesis concerning DMD's developmental delay of attentional skills. We hypothesize a worse performance in attentional tasks of DMDs compared to an age-matched control group, but a similar performance compared to a younger control group (i.e., three years younger).

We used one voluntary and one automatic orienting of attention task (Posner paradigm) which were modified ad hoc with respect to those by De Moura and colleagues. Responses in our tasks were made by just pressing the spacebar (instead of two possible response buttons as in the previous study) and target stimuli were presented in four possible positions arranged in the shape of a cross (instead of two horizontal positions). The rationale of these choices was that we wanted to minimize the bias due to the motor component of response production, given the involvement of dystrophin in motor control and the recruitment of a young control group, and also to be sure that the attentional focus was shifted not only horizontally, but on the whole perceptive field. We used an additional neutral condition, 'no-cue trials', to observe the ability of reaction to unexpected stimuli (vigilance), in both the automatic and voluntary attention task. Three groups: patients with DMD, age-matched healthy controls and younger healthy controls, performed the two attention tasks.