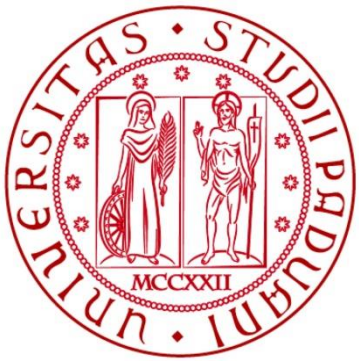

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CURRICULUM NEUROSCIENCES – XXIX CYCLE

EMPATHY AND EXECUTIVE FUNCTIONS IN NEUROMUSCULAR DISEASES

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1. INTRODUCTION

The study of the ability to feel and understand the mental state of others and the more complex cognitive capacities of human brain has been matter of interest both in psychological research and in medical field.

The relationship between these two fundamental constructs has subsequently become evident, considering the performances emerging from neuropsychological assessments and the neural correlates underpinning each one (Pennington & Ozonoff, 1996; Eslinger et al., 2011).

In particular, **Executive Functioning** (EF) seems to be principally related to a particular form of Empathy, the **Cognitive Empathy**, also called mentalizing or **Theory of Mind (ToM)**. ToM is typically defined as the ability whereby an individual attributes mental states to himself and others (Premack and Woodruff, 1978) and it's opposed to **Affective Empathy** (or emotional Empathy), that is the ability to experience and share the emotions of others (Mehrabia, 1972), and it refers to a more primitive form of Empathy, not strictly linked to cognition.

Researchers' attention focused predominantly on diseases in which the impairment of Empathy abilities and EF were particularly evident.

Considering pathologies involving the Central Nervous System (CNS), evidences regarding deficits on ToM skills related to impairment in EF are nowadays well known in **Parkinson disease** and **Alzheimer disease** (Narme et al., 2013; Bodden et al., 2010; Moreau et al., 2015).

Focusing on **Neuromuscular Disorders** (NMD), impairment in ToM abilities emerged from studies investigating **Amyotrophic Lateral Sclerosis** (**ALS**; Cavallo et al., 2011; Abrahams et al., 2011). This deficit seems to be related also to Executive Dysfunction (Girardi et al., 2011; Goldstein & Abrahams, 2013). Similar results arose relatively to patients affected by **Myothonic distrophy, type 1** (**DM1**; Romeo et al., 2010; Kobayakawa et al., 2012). It's important to specify that, even if ALS and DM1 are part of the realm of NMD, the neurological evidences that characterize these two pathologies are partially different relatively to the neurological characteristics of the diseases that will be discussed later, both as regards the cortical and subcortical areas implicated and considering the severity of the involvement.

Considering others NMD, literature highlighted overt or subtle deficits on abilities related to EF, but little or nothing is known about the consequences of these impairments on social functioning and, in particular, on Empathic abilities.

In the light of the findings aforementioned, the aim of the present study was the **evaluation of ToM abilities and its association with Executive Functions (EFs)** in the NMD in which EFs can be compromised, and so: **Duchenne muscular dystrophy (DMD)**, **Becker muscular dystrophy (BMD), Facioscapulohumeral dystrophy (FSHD) and X-linked Spinal and Bulbar Muscular Atrophy (X-SBMA).**

Moreover, also abilities related to Affective Empathy have been investigated.

The study of Empathy and EFs has been carried out starting from particular evidences, specific for each disease considered, derived from literature.

Considering the age of onset of each pathology taken into account in this study and the age of the patients that could be enrolled, it has been chosen to recruit patients affected by BMD, FSHD and X-SBMA of legal age; on the other hand, DMD patients recruited were only underage. For this reason, the tests used to assess Empathy and EFs are different depending on the disease.

As regards the structure of the present work, firstly it will be described accurately what Empathy and EFs are, together with the neural correlates associated to these functions.

Secondly, it will be presented the current literature that regards the relationship between Empathy and EFs in ALS and DM1, two NMD in which this research has already been carried out.

Subsequently, the focus of the attention will be directed to the four NMD considered, with a particular attention on the cognitive profile and the personality traits known thanks to literature.

The expected results were in line with the evidences given by literature, so it was presumed that EFs deficits would be related to problems relatively to ToM abilities with intact Affective Empathy. Moreover, correlations between EFs tests and tasks assessing ToM were expected.

The results of all the studies carried out will be presented separately for each disease; the complementary study conducted with DMD patients and caregivers will be illustrate in chapter 9.

The outcomes will be discussed considering the preliminary hypothesis and the evidences that derive from literature.

The results emerged from this research can give an important contribution to clinical practice: know the Empathic abilities of patients may be useful to clinicians in order to create a good alliance which is extremely useful in the compliance of treatments and therapeutic choices.

2. EMPATHY and EXECUTIVE FUNCTIONS

2.1. EMPATHY

2.1.1. What is empathy?

Empathy is defined as the ability to understand or feel what another person is experiencing (Greenson, 1961; Premack & Woodruff, 1978).
The word empathy derives from the Greek “εμπαθεία" (*empatéia*, composed by *en-*, "in", and *pathos*, "suffering or feeling").

Considering the current literature on this topic, Empathy can’t be described as a unitary construct: it can rather be defined as a multifaceted ability.
One of the most common classification among Authors is the one that distinguishes between **Affective Empathy**, or emotional Empathy, described as *the ability to feel and share the emotions of others* (Mehrabian & Epseitn, 1972; Gallese, 2003; Zaki & Ochsner, 2012), and **Cognitive Empathy**, also called mentalizing, that is *the capacity to understand one’s own and another people’s mental state, as emotions, desires, beliefs, and to refer to them to foresee and explain the behaviour* (Premack & Woodruff, 1978; Zaki & Ochsner, 2012).

Affective Empathy, considered as a phylogenetically early emotional contagion system (Gallese, 2003), allows to recognize the emotions felt by another person and to live it as if it were your own. Emotional Empathy includes Empathy for pain as well (Shamay-Tsoory, 2011).

On the other hand, Cognitive Empathy looks like an advanced cognitive perspective-taking system (De Waal, 2008) and it allows people to make inferences regarding mental states of others. Cognitive Empathy is strictly linked to the concept of **ToM** (Shamay-Tsoory et al., 2009). ToM can be defined as a *social cognitive skill that refers broadly to the capacity to understand others’ mental states and to appreciate that these may differ from our own*’ (Premack & Woodruff, 1978).

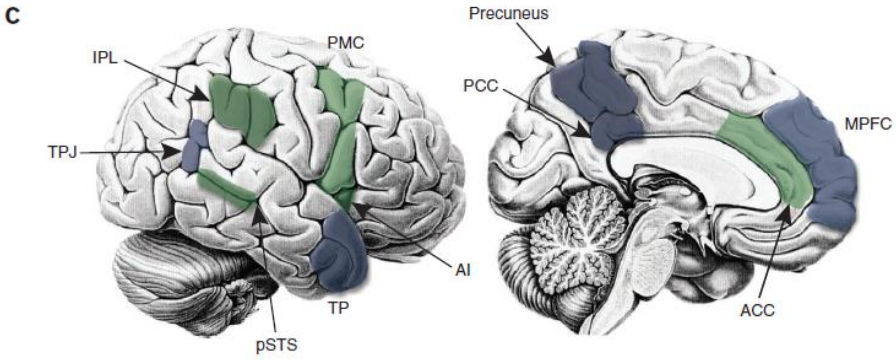
Furthermore, ToM itself can be divided in two subcomponents: Affective ToM and Cognitive ToM (Shamay-Tsoory, 2011). Affective ToM does not coincide with Affective Empathy but is an affective form of mentalizing. It refers to deductions people make regarding other’s emotions. On the

contrary, Cognitive ToM refers to the ability to make inferences specifically about other people's beliefs (Shamay-Tsoory, 2011).

In the present research, it will be taken into account only the distinction between Affective Empathy and Cognitive Empathy and the words Cognitive Empathy and ToM will be used interchangeably.

2.1.2. Cerebral Correlates related to Cognitive Empathy and Affective Empathy

Focusing on Empathy in the broadest sense of the term, the brain regions that result to be particularly active during the execution of tasks created with the aim to assess Empathy abilities include the inferior parietal lobe, the temporo-parietal junction, the posterior superior temporal sulcus, the temporal pole, the anterior insula, the premotor cortex, the anterior and posterior cingulate cortex and the medial prefrontal cortex (Shamay-Tsoory, 2011; Zaki & Ochsner, 2012).



(c) Brain regions associated with experience sharing and mentalizing. IPL, inferior parietal lobule; TPJ, temporoparietal junction; pSTS, posterior superior temporal sulcus; TP, temporal ole; AI, anterior insula; PMC, premotor cortex; PCC, posterior cingulate cortex; ACC, anterior cingulate cortex; MPFC, medial prefrontal cortex.

Shamay-Tsoory, 2011; Zaki & Ochsner, 2012

The distinction between Cognitive Empathy and Affective Empathy can be detectable also considering cerebral areas underpinning these two aspects of Empathy.

More precisely, the neural mediators of Affective Empathy seem to be the inferior frontal gyrus (Schulte-Ruther, 2007), the anterior insula (Wicker, 2003; Singer, 2004), the medial prefrontal cortex, the amygdala, the temporo-parietal junction, the middle and inferior temporal regions, the

paracingulate cortex, the anterior e posterior cingulate cortex (Vollm et al., 2006) and the limbic systems (Zaki & Ochsner, 2012).

On the other hand, the cerebral areas underpinning Cognitive Empathy seem to be the medial prefrontal cortex (Eslinger, 1998; Shamay-Tsoory, 2003), the temporo-parietal junction (Saxe & Kanwisher, 2003), the posterior superior temporal sulcus (Frith and Frith, 2003), the temporal pole (Firth & Firth, 2003), the paracingulate cortex (Gallagher & Frith, 2003) and the precuneus (Zaki & Ochsner, 2012).

It's evident that some areas, as the medial prefrontal cortex, the temporo parietal junction, the temporal poles and the paracingulate cortex, are activated both in Cognitive and Affective Empathy tasks (Vollm et al., 2006).

As regards the neural mediators of ToM tasks, an extensive review of Carrington et al. (2009) highlighted the core regions of the ToM network. The cerebral areas that are more often mentioned by literature in relation to ToM assessment are the medial prefrontal cortex, the orbito frontal cortex and the superior temporal sulcus. These regions are the most commonly activated regardless of paradigm-type. Other areas that contribute to ToM reasoning are the anterior temporal lobe, the temporo-parietal junction and the anterior paracingulate cortices.
Every different type of ToM task seems to activate different cerebral areas. For example, during tasks in which the subject has to recognize mental state terms, the most important areas seem to be OFC and mPFC. It's important to note that no single region is recruited in all neuroimaging studies of ToM because of the heterogeneity of the tasks used to assess ToM abilities (Carrington et al., 2009).

An extremely interesting study carried by Shamay-Tsoory (2009) demonstrated not only that Affective Empathy and ToM are related to separate anatomical substrates but it also showed an anatomical and behavioral double dissociation. These results emerged from a depth investigation on people with lesion in the ventromedial prefrontal cortex or inferior frontal gyrus damage.
From Shamay-Tsoory investigation emerged that ventromedial prefrontal cortex lesion leads to deficit exclusively in tests assessing mentalizing while a damage on inferior frontal gyrus conducted to problems only on tasks evaluating Affective Empathy. These evidences supported the theory of the independence of Affective Empathy and Cognitive Empathy because of their different neural mediators.

Also Diozbek et al. (2014) found a dissociation between the two subcomponents of Empathy. This evidence arose thanks to the examination of patients impaired only in Affective Empathy or in Cognitive Empathy abilities.

Each area mentioned above, related to Empathy functioning, is implicated in the elaboration of specific types of information. Here a brief description of the most important one:

- **The medial Prefrontal Cortex** seems to play a general role in the representation of socially relevant information about others. Specifically, the dorsal region is involved in the representation of thoughts and feelings of others while the ventral region is linked to the representation of one's mind and in self-awareness. This area stores the emotional value of an action (Damasio et al., 1996; Sharot et al., 2007; Mitchell et al., 2005 & 2006);
- **The Superior Temporal Sulcus** results active when an animal is monitoring the direction of gaze of others (Campbell et al., 1990) and it's involved in the observation of biological motion (Allison et al., 2000; Bonda et al., 1996; Grossman et al., 2000);
- **The Temporo Parietal Junction** is crucial in false belief reasoning (Kobayashy et al., 2007; Carrington & Bailey, 2009). Indeed, the right side seems to be implicated during the judgment of the intentions and beliefs of others (Blanke & Arzy, 2005; Farrer et al., 2003; Farrer & Frith, 2002) highlighting the importance of this region in monitoring themselves and others;
- **The Orbito Frontal Cortex** seems to be essential to judge pragmatic aspects as a gaffe, in social judgment and during inhibition (Baron-Cohen, 1994);
- **The Anterior Cingulate Cortex** is activated when a person sees the pain of others and is a part of the pain matrix (Hutchinson & Davis, 1999). It's implicated also in action monitoring and detection of errors (Bush et al., 2000);
- **The Amygdala** has the function of regulate emotions and mediate emotional learning (Siegel & Weinberger, 2009). A lesion in this area leads to inability to recognize emotions of fear in others (Shaw et al. 2004);

2.1.3. Disorders related to Empathy impairment

Empathy has been studied considering diseases that principally affect the functioning of this ability, such as Autistic Spectrum Disorders (ASD). Autism is defined as the presence of markedly abnormal or impaired development in social interaction and communication and a significantly restricted repertoire of activity and interest (DSM-IV).

Usually, people affected by ASD lack of Empathy, have a deficit regarding the ability to represent mental states of others (Baron-Cohen & Robertson, 1995), don't understand false belief (mind-blindness), are not good in deception (Sodian & Frith, 1992), and don't use words that indicate beliefs and ideas (Tager-Flusberg, 1992).

These deficits are not related to impairment in EF: actually, some high-functioning autistic people have normal abilities regarding EFs (Ring et al., 1999).

Only social brain areas are identified as the most discriminative between people affected by ASD and healthy persons. A functional Magnetic Resonance Imaging (fMRI) study conducted by Chanel et al. (2006) involving ASD patients performing social tasks, identified as the most discriminative areas between autistic person and healthy controls the regions related to social cognition and involved in the processing of faces and bodies: these areas were the fusiform face area, the occipital face area, the extrastriate body area, the superior temporal sulcus, the temporo parietal junction and the premotor cortex. All these regions showed reduced contribution in ASD participants compared to controls.

Moreover, early brain lesions can selectively impair ToM abilities without impairing EF. A study of Fine et al. (2001) revealed, in a patient with early and congenital left amygdala damage, a severe impairment in representing mental states of others but no deficits relatively to EFs.

2.2. EXECUTIVE FUNCTIONS

2.2.1 What are Executive Functions?

The EFs of the brain are the complex processes by which an individual optimizes his or her performance in a situation that requires operation of a number of cognitive processes (Baddeley, 1986). These processes are the brains' conductor, which instructs other regions to perform, or be silenced, and generally coordinates their synchronized activity (Goldberg, 2001).

EFs can be seen as a multifaceted construct that involves a variety of high-level cognitive abilities (De Frias et al., 2006).

It's well known that EFs are not related to one particular domain but take on the role of supervising and controlling.

There is a general agreement relatively to the three core aspects of EFs (Lehto et al., 2003; Miyake et al., 2000), that are:

- Inhibition (inhibitory control, including self-control and interference control);
- Working Memory;
- Cognitive Flexibility (including creative thinking, seeing anything from different perspectives and flexibly adapting to changed circumstances) (Diamond, 2013).

From these core topics, higher-order EFs are built such as reasoning, problem solving and planning (Collins & Koechlin, 2012; Lunt et al, 2012).

Nowadays, it's well known that the utility of EFs is widespread and complex. EFs are activated:

- in situations in which the automatic response can't work and there's the need to choose the more correct response considering the situation;
- when there's the need to optimize the performance in situations of planning and decision making,
- in conditions in which errors must be corrected or when the responses are not well learned or contain novel sequences of actions;
- when there is the need to judge, especially if a situation is dangerous or difficult;
- in conditions that require overcoming of a strong habitual response or resisting temptation (Barkley, 1997; Miyake et al., 2000; Zelazo & Müller, 2002).

2.2.2. Cerebral Correlates related to EFs

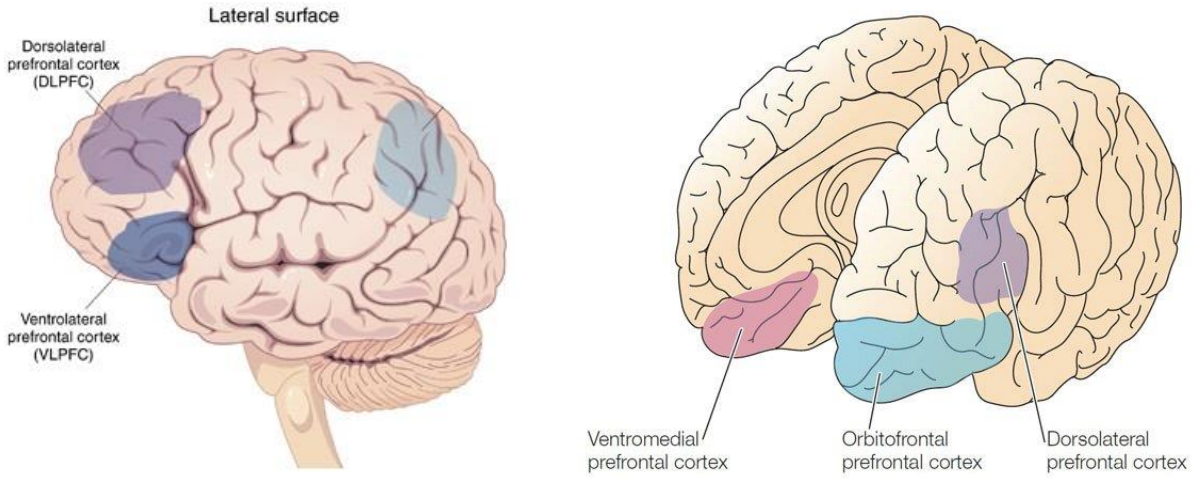
EFs are related to various distributed networks, which include frontal and posterior regions of the cerebral cortex, as well as subcortical regions (Chung et al., 2014; Colette et al., 2006; Jurado & Rosselli, 2007). Particularly involved are the prefrontal regions of the frontal lobes and parietal regions (Alvarez, 2006; Badre & Wagner, 2007; Collette et al., 2005; Gilbert et al, 2008; Jacobs et al., 2011; Tamnes et al., 2010; Van Petten et al., 2004).

Even if many cerebral areas are activated during the performance of a cognitive task, there is some degree of functional specialization within the network of EFs. The degree is likely to be relative rather than absolute. For example, the same prefrontal regions are recruited by a wide variety of tasks (Duncan & Owen, 2000).

Here a brief description of the cerebral areas typically involved in EF:

- The **dorso lateral Prefrontal Cortex** is implicated in planning an action, performing for trials and errors (Morris et al., 1997) and has a role in selecting and manipulating information in the Working Memory during planning.
  More in depth, the **left dorso lateral Prefrontal Cortex** is involved in response selection and free choice, highlighting the range of the possible responses and suppressing the inappropriate one (Frith, 2000). It supports the generation of random sequences (Jahanshahi et al., 2000) and task switching (Dreher & Grafman, 2003).
  On the other hand, the **right dorso lateral Prefrontal Cortex** is implicated in the monitoring of the content of internally held information (Habib et al., 2003) and the object of externally presented information, such as tasks of sustained attention (Kanwisher & Wojciulik, 2000). For these reasons, greater activity of this area can be seen in condition of uncertainty;
- The **ventro lateral Prefrontal Cortex** is associated to rule changes following feedback that the response was incorrect, for example in the Wisconsin Card Sorting Test, maintenance of information in Working Memory and is implicated in the activation of stored knowledge to facilitate decisions. **Left ventro lateral Prefrontal Cortex** is the area where words are memorized (Wagner et al., 1998) while **right ventro lateral Prefrontal Cortex** refers to

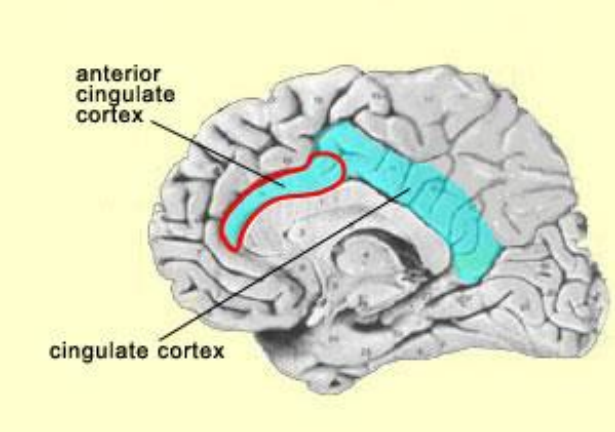
colored visual texture, is active during spatial Working Memory tests (Manoach et al., 2004) and has a role in inhibition of both verbal and motor responses (Aron et al., 2004);



Jack W. Bradbury & Sandra L. Vehrencamp, 2011

- The **ventro medial Prefrontal Cortex** is implicated in the processing of risk and fear and regulation of emotions (Hansel et al., 2008). It also plays a role in the inhibition of emotional responses and in the process of decision making (Bechara et al., 2000);
- The **Orbito Frontal Cortex** plays a key role in impulse control, maintenance of set, monitoring ongoing behavior and socially appropriate conducts (Lezak et al., 2004);
- The **left Prefrontal Cortex** is essential when there's the need to develop strategies for dealing with novel situations. This area is active during verbal fluency task (Chung et al., 2014);
- The **Anterior Prefrontal Cortex** is implicated in the coordination of goals and subgoals; it's also involved in multi-tasking (Ramnani et al., 2004);
- The **Anterior Cingulate Cortex** is associated with response conflict and the overcoming of habitual responses. The **dorsal region** is engaged during the detection of errors (Carter et al., 1998), so patients with lesions in this area are not able to make no adjustment after

committing errors. Moreover, this area is involved in evaluating response conflict (Stroop, 1935) and in dual task (Dreher & Grafman, 2003).



Dr. Louann Brizendine, 2014

2.2.3. Disorders related to Executive Dysfunction

Considering the degree of specialization of EFs and the fact that this construct develops later in comparison with other cognitive abilities, it's easy to understand why deficits on one or more of the skills supported by EFs are frequently observed in many diseases. Pathologies that include in their symptoms Executive Dysfunctions can be present from the birth, be acquired because of brain damage or develop during lifetime, often in old age.

Attention-Deficit/Hyperactivity Disorder (ADHD) is a disease that develops in childhood and is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development (DSM-V). These symptoms reduce QoL, as well as social, academic and occupational functioning of the patient affected.

They have been noticed, in ADHD patients, deficits on Working Memory, inhibition (Nigg, 1999) self-regulation of affect, internalization of speech and reconstitution (that is behavioral analysis and synthesis) (Barkley, 1997) and delay aversion (the tendency to choose a smaller immediate reward rather than wait for a larger delayed reward) (Dalen et al., 2004; Solanto et al., 2001; Sonuga-Barke et al., 2003). Even though the precise causes of ADHD are already unknown, it's clear that the main aspect of the disease is the Executive Dysfunction that affects most patients.

Another disease that affects EFs is Fronto Temporal Dementia (FTD). FTD is the second most common early-onset dementia and is clinically characterized by progressive behavioral changes,

frontal executive deficits and/or selective language difficulties (Neary et al., 2005). The disease progresses from an insidious onset of behavioral change or language impairment and cognitive decline to a severe and more generalized dementia, accompanied by progressive atrophy of frontal and temporal lobes (Bott et al., 2014).

Impairment of EFs, including planning, organization, judgement, problem solving and mental flexibility, is a main feature of FTD (Gregory et al., 1996).

In particular, patients with FTD manifest high numbers of rule violations on the Tower Test compared to healthy controls (Carey et al., 2008) and impaired performance on the Delis-Kaplan Executive Functions System Sorting Test associated with decreased left frontal lobe volume (Fine et al., 2008). Moreover, letter fluency is impaired in patients with left prefrontal lesions (Baldo et al., 2006), as digit span and inhibition of prepotent responses (Hornberger et al., 2008).

2.3 THE RELATION BETWEEN COGNITIVE EMPATHY and EXECUTIVE FUNCTIONS

The development of ToM seems to be related to the integrity of EFs.

In literature, there have been frequent claims that ToM is mediated by general EF (Russell, 1997), with this relation staring during childhood (Carlson et al., 2002).

The relation between ToM and EF is evident also in the diseases aforementioned.

For example, in patients affected by ASD, characterized by deficits on Empathic abilities, it can be observed an impairment also in EF, even if not in all cases (Hill, 2004). These deficits seem to affect inhibitory control, set shifting (Schmitz et al., 2006), self-monitoring and planning (Robinson et al., 2009). Moreover, in a study of Happé et al. (2006) emerged that ASD patients performed significantly worse on response selection/monitoring in a cognitive estimates task; EFs scores resulted to be related to specific aspects of communicative and social adaptation.

The characteristic features of ASD patients result to be independent of IQ and verbal ability (Robinson et al., 2009).

On the other hand, patients affected by FTD, manifesting various deficits on EF, show marked impairments in mentalizing.

Literature highlights deficits on moral reasoning with spared knowledge of social rules. Empathy, as rated by carers, was also shown to be abnormal (Lough et al., 2006). Moreover, emotion recognition seems to be globally impaired in FTD patients affected by the behavioral variant (Baez et al., 2014).

Even if in these diseases are present impairments both on Empathy abilities and EF, the two constructs taken into account don't always go on the same direction. For example, there are cases, in patients affected by ASD, in which there's an evident impairment in ToM abilities with spared EF (Baron-Cohen et al., 1999).

Moreover, the neural correlates of ToM and EF are only partially overlapping (Russell, 1997; Eslinger, 1998; Carlson & Moses, 2002; Firth and Firth, 2003; Wicker, 2003; Shamay-Tsoory, 2003; Saxe and Kanwisher, 2003; Singer, 2004; Collette, 2005; Badre & Wagner, 2007; Gilbert, 2008; Chung, 2014), thus confirming the impossibility to overlap the two constructs.

The study of Empathy and EF has been already carried out in some diseases of the CNS.
In the next chapter it will be discussed this topic relatively to two NMD: the ALS and the DM1.

As mentioned in the introduction, the neural correlates that characterize these two pathologies are partially different from the neuroimaging evidences that emerged from literature regarding DMD, BMD, FSHD and SBMA. Nevertheless, there are some neurological similarities for which it can be interesting, as a premise, discuss about EFs and Empathy in ALS and DM 1, before starting the investigation of the other pathologies.

3. AMYOTROPHIC LATERAL SCLEROSIS and MYOTONIC DYSTROPHY type 1

3.1. AMYOTROPHIC LATERAL SCLEROSIS

3.1.1. The disease

ALS is the most known MND.

MND are caused by progressive neurodegeneration and loss of motor neuron at central level (upper motor neuron in the cortex) and peripheral (lower motor neuron in the trunk of the brain and spinal cord) that typically leads to decrease of muscular strength and muscular atrophy (Leigh and Ray-Chaudhuri, 1994).

ASL is a rare pathology that affects almost 3.9 persons in 100.000 individuals (Mehta et al., 2014) and its etiology is almost unknown.
The most common cause of ALS is a mutation of the gene encoding the antioxidant enzyme superoxide dismutase 1 (SOD1) (Dangoumau et al., 2014; Pasinelli et al., 2004). Mutant SOD1 has a structural instability that causes a misfold in the mutated enzyme, which can lead to aggregation in the motor neurons within the CNS (Forsberg et al., 2011). The most important hypothesis regarding the mechanism underlying the mode of action of mutant SOD include the glutamate excitotoxicity (Forsberg et al., 2011), structural and functional abnormalities in mitochondria (De Vos et al., 2000; Jaiswal et al., 2014), impaired axonal structure or transport defects (Magranè et al., 2008), and free radical-mediated oxidative stress (Mitsumoto et al., 2014).

The age of onset of ALS is typically between 50 and 65 years (Abrahams, 2011; Logroscino et al., 2008). Only 5% of the cases have an onset prior to thirty years old (Logroscino et al., 2010).

ASL can be categorized in two forms: the most common is the sporadic one, that affects almost 90-95% of ALS patients and has no obvious genetically inherited component. On the other hand, 5-10% of patients are affected by a familial-type ALS (FALS) due to their associated genetic dominant inheritance factor (Abhinav et al., 2007).

The different ALS phenotypes are classified mainly as: limb onset, bulbar onset, progressive muscular atrophy (PMA), progressive bulbar palsy (PBP) and primary lateral sclerosis (PLS) (Kiernan et al., 2011; Wijesekera et al., 2009).

The most common symptoms for ALS patients are muscle weakness, twitching and cramping, which subsequentially leads to the impairment of muscles (Goetz et al., 2000). ALS patients experience localized muscle weakness that begins distally or proximally in their upper and lower limbs (Zarei et al., 2015). Usually, the onset symptoms are asymmetric and develop in progressive generalized weakness and wasting of the muscles. The majority of the patients develop bulbar and respiratory symptoms and spasticity (Goetz et al., 2000). Muscle atrophy, including muscle of hands, forearms or shoulders, and proximal thigh or distal foot muscle in lower limbs, is usually discovered early in the development of limb-onset ALS (Vucis et al., 2007).

In patients with bulbar symptoms can be observed sialorrhea, due to an irreversible loss of the ability to swallow (dysphagia), and dysarthria, so difficulties regarding the articulation of words.

The presence of respiratory weakness leads to respiratory failure, nocturnal hypoventilation including dyspnea, orthopnea, disturbed sleep, excessive somnolence in daytime, morning headaches, irritability and mood changes (Polkey et a., 1999).

Without any treatment, the average survival after the onset of symptoms of ALS is three - five years (Hardiman et al., 2011; Magnus et al., 2002) and the main cause of death in ASL is respiratory failure as the results of pulmonary complication (Corcia et al., 2008).

Nowadays, there’s no cure for this debilitating disease. Patients can be treated with Riluzole that is the only FDA-approved drug treatment identified to have beneficial use in the survival of ALS patients (Bensimon et al., 2002).

Development of depression is one of the most common secondary symptoms associated with ALS (Blatzheim, 2009). The prevalence of depression is of 4-56% depending on the assessment measures (Hammer et al., 2008; Rabkin et al., 2005). Moreover, it has been evidenced, in a cohort of ALS patients, a prevalence of 29% of mild depression and a prevalence of 6% of severe depression; depression seems not to be related to advanced ALS or approaching end of life (Kubler et al., 2005). Behavioral changes, such as irritability, disinhibition and apathy are more present in ALS patients if compared to healthy population (Lomeh & Hoerth, 2003; Grossman et al., 2007; Morphy et al., 2007).

Frontal syndrome is evident in 50% of ALS patients and it's similar to the profile that characterize FTD (Ferrari et al., 2011).

3.1.2. Cognitive profile

As regards cognition, mild to moderate cognitive impairment is present from 32% to 36% of ALS patients (Abrahams et al., 2004; Massman et al., 1996; Ringholz et al., 2005), principally involving attention and EF (more precisely: rule deduction, cognitive flexibility, monitoring and switching). It results to be particularly impaired the test assessing verbal fluency (Abrahams et al., 2000; Abrahams, Leigh & Goldstein, 2005; Massman et al., 1996; Osborne et al., 2014; Phukan et al., 2007 & 2011; Pinkhardt et al., 2008). The compromised performance on verbal fluency is present early in the disease course (Abrahams et al., 2005) and is more pronounced in ALS patients with PBP variant (Abrahams & Goldstein, 1997) relatively to ALS patients affected by other variants.
Interestingly, patients with a bulbar onset of the disease show poorer performance on almost all the neuropsychological tasks compared to controls and to patients without bulbar signs (Gibbons et al., 2007; Raaphorst et al., 2010).

Using an instrument specifically created by Abrahams et coll. (2014), the Edinburg Cognitive and Behavioral ALS Screen (ECAS), with the aim to detect cognitive impairment in ALS patients, Authors highlighted that 29% of tested patients showed abnormal ALS-specific scores and 6% of the group also showed abnormal performance on ALS non-specific tests. The most prevalent deficit occurred in language functions (35%) followed by EFs and fluency (23% each). Forty percent of careers reported behavioral change in their relatives affected by ALS in at least one domain, while 15% of patients met criteria for possible FTD (Abrahams et al., 2014).

Focusing on EF, 25-50% of nondemented ASL patients show cognitive impairment in EF (Abrahams & Goldstein, 2002; Strong et al., 2009). Patients with Executive Dysfunction seem to be older at symptoms onset and have a more rapid disease progression (Phukan et al., 2011). Interestingly, a little percentage of ALS patients can show cognitive impairment without Executive Dysfunctions (Phukan et al., 2011).

Considering neuroimaging studies, literature highlights evidences of abnormalities in frontal lobe (Abrahams et al., 1996; Ludoplh et al., 1992; Talbot et al., 1995), as well as degenerative changes in

the prefrontal cortex (Maekawa et al., 2004), in particular in dorso lateral prefrontal cortex and anterior cingulate cortex gyrus (Abrahams et al., 1996 & 2004). Finally, it has been showed frontotemporal white matter abnormalities (Abrahams et al., 2005).

3.1.3. Empathy and Social Cognition

As regards Empathy abilities, a study conducted by Hulst & Abrahams (2014) revealed that the participants affected by ALS had impaired Empathy skills if compared with healthy controls. Considering the sample, 36% demonstrated a deficit related to Affective Empathy abilities, while 27% of the sample showed impairments in Cognitive Empathy skills. Beyond reduced Empathy, there was evidences of increased behavioral dysfunction and high levels of apathy.
Moreover, ALS patients with Affective or Cognitive Empathy deficits exhibited poor self-awareness of their performance. Finally, this subgroup of patients manifested also abnormalities on verbal fluency.

Many Authors confirmed the presence of impaired performance on ToM tests in ALS patients (Gregory et al., 2002, Lough et al., 2006; Snowden et al., 2003, Torralva et al., 2007).
Interestingly, ToM deficits seem to be more prominent in ALS patients with bulbar symptoms (Abrahams, 2012).

Focusing on the research of Schmolck et al. (2007), in which ALS patients had to perform on a test with the aim to judge the approachability of unfamiliar faces, it emerged that more than half of the evaluated patients had similar behavioral characteristic to patients with bilateral amygdala damage, so they showed an inability to recognize threat in a given social context. Patients rated faces as more approachable than controls and rated the 10 most negative faces much more positively.
In ALS patients, the emotional processing *per se* seems to be compromised, with consequent impairment in emotional recognition (Lough et al., 2006). The emotional processing deficit appears to be selective and is not a manifestation of general cognitive decline or attentional dysfunction (Papps et al., 2005).

Moreover, ALS patients result to be impaired in their ability to understand others' behavior in social situations using the Faux Pas task (Cavallo et al., 2011; Meier et al., 2010). They exhibit difficulties

in inhibiting egocentric responding and in the use of simple social cues, such as eye-gaze, to perform the tasks effectively (Snowden et al., 2007).

Considering behavioral characteristic, ALS patients can display self-centeredness, selfishness, aggression, social disinhibition and loss of insight (Gibbons et al.,2008).

As regards neuroimaging evidences, an fMRI study conducted by Grossmann et al. (2008) attested significant cortical atrophy in ALS patients in frontal lobe bilaterally and in the motor and premotor cortex. It appears that the large-scale neural network underlying action concepts is interrupted in these patients.

3.1.4. Amyotrophic Lateral Sclerosis and Fronto Temporal Dementia

Since the second decade of 1800, it's known that patients affected by ALS may show FTD signs (Ferrari et al., 2011) but the definition of ALS-FTD has been formalized only recently in Neary criteria (1998) and Strong criteria (2009).
The subclinical sings of FTD that can be shown by ALS patients are behavioral, cognitive and language dysfunctions (Strong, 2008).
In particular, clinical overlap between ALS and FTD can be assessed by subclinical frontal dysfunction or language impairment (Abrahams et al., 2004; Lillo et al., 2010; Mackenzie et al., 2005; Phukan et al., 2011) but the majority of ALS-FTD patients present with behavioral changes, typical of the behavioral variant of FTD (bv-FTD) (Phukan et al., 2011).
The frequency of FTD symptoms in ALS patients can vary from 5% to 40% (Strong, 2008); however, some symptoms of FTD can be detected in up to 50% of ALS patients (Liscic et al., 2008; Lomen-Hoerth et al., 2002 & 2003; Strong, 2008; Strong et al., 2003).
Shorter survival rate can be observed in patients affected by ALS-FTD relatively to ALS patients without FTD (Van Damme et al., 2009). Moreover, ALS patients with FTD and subtler behavioral disturbances have significantly more grey matter volume reductions in the right hemisphere in comparison with ALS patients without cognitive or behavioral problems (Murphy et al., 2007).

On the other hand, about 5-10% of FTD patients develop ALS signs (Goldman et al., 2005; Johnson et al., 2005; Seelaar et al., 2007).

As mentioned in the previous chapter, FTD patients have been found to perform poorly on ToM tests, even in early stages of the disease (Eslinger et al., 2001; Gregory et al., 2002; Lough et al., 2006; Snowden et al., 2003) and also in Empathy and emotion recognition (Lough et al., 2006; Shamay-Tsoory et al., 2007).
General executive deficits may contribute to FTD patients' impaired performance (Channon & Crawford, 2000; Saltzman et al., 2000).

Comprehensibly, the presence of FTD together with ALS increases the risk of deterioration of social relationship between the patients and the careers (Abrahams, 2011).

3.2. MYOTONIC DYSTROPHY type 1

3.2.1. The disease

Myotonic Dystrophies (DM) are the muscular dystrophies with adult onset with higher prevalence; they are genetic multisystemic diseases that affect several muscle groups (Richer et al., 1994; Meola et al., 1996).

DM can be divided in two types: DM1 (or Steiner disease) and DM2 (PROMM).
DM1 is caused by the expansion-mutation of the trinucleotide CGT in the 19 chromosome of DMPK gene. CGT repeat length exceeding 34 repeats is abnormal: specifically, repeats between 35 and 49 lead to no symptoms while more than 50 CGT repeats lead to full penetrance alleles and disease manifestation (Brook et al., 1992; Martorell et al., 2001). There is considerable somatic mosaicism for the size of the CTG expansion between various organs (Moxley & Meola, 2008).
Larger the expansion is, graver will be the clinical expression of the disease and earlier the onset (De Temmerman et al., 2004; Rakocevic-Stojanovic et al., 2005).
DM1 can be divided in four main categories, each presenting specific clinical features and management problems: congenital, childhood-onset, adult-onset and late-onset/asymptomatic (Meola & Cardani, 2015).

DM2 is caused by the expansion-mutation of the tetranucleotide CCGT in the CNBP gene (Liquori et al., 2001). The number of CCGT repeats in expanded alleles ranges from 75 to more than 11000, with a mean of approximately 5000 repeats.
Neither the size of a predominant allele nor the total number of different detectable expansions in a single sample can predict disease severity, age of onset or clinical symptoms. Also in DM2, it's evident the presence of marked somatic mosaicism (Day et al., 2003).

DM are hereditary diseases that are transmitted with an autosomal dominant mechanism, so both male and female can be affected with 50% of the offspring of an affected individual having the chance of inheriting the expanded allele. The pathology affects mainly women that also show an earlier age of onset in comparison with men (Lavedan et al., 1993; Romeo et al, 2010).

The onset is typically in the third decade but DM1 can be evident also in childhood. Early age of onset and decreased survival correlate with larger repeat expansion (Groh et al., 2011).

Both patients affect by DM1 or DM2 show signs of myotonia, muscle dysfunction (weakness, pain and stiffness) of skeletal and cardiac muscles, early-onset cataracts and CNS dysfunction (Meola & Sansone, 2007).
In DM2 it can be evident testicular failure resulting in male infertility and need of testosterone replacement therapy for hypogonadism (Day et al., 2003; Savkur et al., 2004). DM2 patients are usually less impaired compared to DM1 patients as regards physical disability (Meola & Cardani, 2015).

The most robust difference between DM1 and DM2 is that neonatal weakness, respiratory failure, mental retardation, craniofacial abnormalities have been reported only in individuals affected by DM1. Moreover, adults with DM1 often have more weakness and myotonia than adults affected by DM2. Finally, there's not a congenital form in DM2 (Day et al., 2003).

DM1 incidence is about 1 every 20.000 born alive (Theadom et al., 2014) and the illness has a prevalence of 1/8000 (Harper, 2001) while DM2 occurs at a higher age and has a prevalence of 1/1830 (Suominen et al., 2011).

Actually, there's not curative therapy, even if patients can be treated with various actions with the aim to control and prevent single symptoms (Benhayon et al., 2015; Johnson et al., 2015).

3.2.2. Cognitive profile

An important clinical difference between DM1 and DM2 is the degree of cognitive impairment.

DM1 may present with a congenital form with a very early and severe onset. Mental retardation can be present from 10% to 24% of cases. Overall full-scale IQ tend to be lower in individuals with classic and mild DM1 (Jean et al., 2014).

Specifically, DM1 patients with a congenital form frequently show delay in cognitive milestones and develop learning difficulties that require special need schooling. Moreover, cerebral atrophy and ventricular enlargement are often present at birth (Ashizawa, 1998; Sprenger et al., 1997).

DM1 childhood-onset often presents with cognitive deficits, learning abnormalities and degenerative features (Steyaert et al., 2000).
Adult-onset DM1 evidences CNS dysfunction with a characteristic of cognitive and neuroimaging involvement (Bugiardini et al., 2014) while there's not evidences of cognitive impairment in DM1 late-onset (Meola & Cardani, 2015).

Mental retardation is present in a less frequent and less severe way in patients affected by DM2 and consists mainly in problems regarding attention, memory, constructive/visual/spatial abilities and reasoning (Ranum et al., 2002; Romeo et al., 2010; Zalonis et al., 2010). DM2 retarded individuals have been reported but this occurrence may be either accidental or an infrequent disease consequence (Day et al., 2003; Ricker et al., 1995).

Mondoni et al. (2008) noted, in DM1 patients, a decline in the functioning of the frontal and temporal lobes linked to age, resulting in deterioration of the global cognitive performance over time and cognitive impairment similar to that caused by FTD, mainly characterized by impairment of language abilities and EFs. Moreover, the number of CTG repeats seems to be correlated with global cognitive intelligence, even if data are controversial (Meola & Sansone, 2007; Sisitaga et al., 2010).

Also Meola et al. (2003) highlighted that DM1 and DM2 patients had significantly lower scores on tests of frontal lobe function compared to controls. Neuropsychiatric interviews demonstrated an avoidant trait personality disorder in both patient groups.

Many neuroimaging evidences report atrophy and white matter abnormalities in DM1 patients (Caso et al., 2014; Meola & Sansone, 2007; Romeo et al., 2010; Wozniak et al., 2013), in particular in the anterior temporal area (Bachmann, 1996; Di Costanzo et al., 2002; Kornblum et al., 2004; Miaux, 1997) and in the superior and middle temporal gyri (Antonini et al., 2004; Giorgio et al., 2006; Ota, 2006). Abnormalities are present in the amygdala, the hippocampus and the entorhinal cortex (Mizukami et al.,1999; Ogata et al., 1998; Oyamada et al., 2006), together with frontal and parietal lesions (Antonini et al., 2004; Giorgio et al., 2006; Ota, 2006).
Finally, a brain single photon emission computed tomography study (SPECT) conducted by Meola et al. (2003) showed frontal and parieto-occipital hypoperfusion while the study of Angelini et al.

(2009) showed minimal hypoperfusion in the posterior cortex planes in DM1 and, to a lesser extent, in DM2.

3.2.3. Empathy and Social Cognition

As regards the behavior and the personality of DM1 patients, literature reports change in their temperament: frequently these patients manifest loss of cooperation and Empathy, harm avoidance, like-schizophrenic behavior, paranoid and aggressive traits and obsessive-compulsive personality (Delaporte, 1998; Peric et al., 2014; Sistiaga et al., 2010; Winblad et al., 2005).
Behavioral problems are a common feature, in particular in DM1 patients with onset in youth or adulthood (Bird et al., 1983; Delaporte, 1998; Winblad et al., 2005) and almost 27% of DM1 patients present high risk of developing a psychiatric disorder (Bertrand et al., 2015).

DM1 patients seem to express a really higher frequency of ADHD and anxiety disorders in comparison to normal population (Antonini et al., 2009; Douniol et al., 2009) and they are more at risk to develop ASD, especially as regards patients with congenital/childhood-onset DM1 (Steyaert et al., 1997; Yoshimura et al., 1989).
Interestingly, the frequency of ASD increases with the number of CTG repeat expansions (Ekstrom et al., 2008).

As discussed previously, skills like Empathy, see things from others' points of view and recognition of facial expressions all share the Empathy networks, so if the cerebral areas that implement Empathy are damaged by the disease there will be, as result, problems in social functioning.

Neuroimaging evidences highlight white matter lesions in the temporal and frontal level (Kobayakawa et al., 2010; Takeda et al., 2009), as well as atrophy of multiple cortical areas, mainly those appointed to control the psychological and emotional functions, such as the recognition of facial emotions (Antonini et al., 2004; Winblad et al., 2006) and the areas involved in the neural networks related to Empathy.

DM1 patients who exhibit lower sensitivity to facial emotions were found to have lesions in the anterior temporal white matter, amygdala, insular region and orbitofrontal cortex (Takeda et al., 2009). Moreover, there are evidences of glutamatergic neuronal degeneration in frontal cortex and in the white matter (Takado et al., 2015).

Considering empathic abilities, DM1 patients results to be impaired both in tests assessing Affective Empathy and in tasks evaluating Cognitive Empathy, but the deficits are more prominent relatively to Affective Empathy (Kobayakawa et al., 2012).
Patients show difficulty in understanding others' mental states from both interactions with others in everyday situations and from their facial expressions.
DM1 patients seem to be impaired in the understanding the context of social interactions and are less sensitive to the emotional impact on other people (Kobayakawa et al., 2012).

All the results presented relatively to Empathy and Social Cognition are referred to patients affected by DM1 because currently there are not evidences of such impairments in DM2 patients (Meola & Cardani, 2015).

The studies just described conducted with the aim to investigate EFs, Empathy abilities and their relation in ALS and DM1 allowed us to have a start point from which begin our research on other NMD.

4. NEUROMUSCULAR DISEASES

4.1. DUCHENNE MUSCULAR DYSTROPHY

4.1.1. The disease

DMD is the most common form of inherited muscle disease in childhood.
It is a X-linked recessive genetic disorder that is caused by the mutation of the dystrophin gene. It affects only male and approximately 30% of cases arise from spontaneous mutations (Emery, 1987).

The dystrophin is an essential transmembrane muscle protein in the dystrophin-glycoprotein complex (Koening et al., 1987). Dystrophin acts as a direct signaling molecule. In muscles, this protein complex spans the membrane, organizes functional membrane microdomains and effectively provides structural stability by linking the cytoskeleton to the extracellular matrix (Wingeier et al., 2011). The lack of dystrophin protein compromises the structural integrity of muscle cells and leads to progressive muscle necrosis (Adams & Victor, 2006).

The pooled prevalence of DMD is 4.78 cases per 100.000 males while the incidence ranges from 10.71 to 27.78 per 100.000 males (Mah et al., 2014).
The age of onset of the firsts symptoms is nearly 30 months (Ciafaloni et al., 2009) and the disease is noted principally because caregivers observe that their child's physical ability diverges markedly from that of his peers.

In particular, affected individuals can have mildly delayed motor milestones and most are unable to run or jump properly due to proximal muscle weakness, which results also in the use of the classic Gowers' manoeuvre when arising from the floor (Bushby et al., 2009).
These pediatric patients are affected by progressive muscular weakness that leads to loss of ambulation between 8 and 12 years. Respiratory and cardiac complications emerge, as well as contractures and spinal deformity; gradually, all muscle groups are impacted (Brody 1968; Emery 1991).

During adolescence, ventilation is usually necessary for breathing difficulties, so that DMD patients become totally dependent upon caregivers for basic self-care (Emery, 2001).

Death, commonly caused by respiratory or cardiac complications, typically occurs by the early twenties (Bushby et al., 2009).

There are some medical managements in order to slow the progression of the muscular weakness, as the corticosteroid therapy that prolong ambulation and rehabilitative interventions that lead to improvement in function, QoL and longevity. Unfortunately, no cure is currently available.

4.1.2. Cognitive profile

The mutation that causes the absence of dystrophin is present also in the CNS, particularly in the cerebral cortex and cerebellum, proving that DMD is a disorder that affects also the brain (Anderson et al., 2002).
Probably, synaptic functioning is influenced by dystrophin absence at neural level. Dystrophin seems to be generically involved in normal synaptic terminal integrity, synaptic plasticity and regional cellular signal integration (Blake & Kroger, 2000; Carlson, 1998; Muntoni et al., 2003).
The lack of dystrophin in the CNS is associated to cognitive deficit in one third of DMD patients. Cognitive deficit is not progressive and is not related to muscular weakness (D'Angelo et al., 2006).

Moreover, several neuroimaging studies involving DMD patients showed disorders in CNS architecture, as dendritic abnormalities, neuronal loss, cortical atrophy (especially in older patients) and loss of Purkinje cells (Blake et al., 2000; Mehler et al., 2000).
These brain anomalies, however, are not present in all the DMD patients tested (Anderson et al., 2002).

As regards the type of dystrophin mutation, an extremely interesting study of D'Angelo et al. (2011) revealed that DMD patients with mutations located in the distal portion of the dystrophin gene, so involving the Dp140 brain protein isoform, were generally more severely affected and expressed different patterns of strength and impairments relatively to DMD patients with mutations located in the proximal portion of the dystrophin gene, not involving Dp140 isoform.

DMD patients with distal mutations demonstrated specific impairments in visuospatial functions, visual memory and greater impairment in syntactic processing. (D'Angelo et al., 2011).

Considering the cognitive impairment that can be present in DMD patients, it seems that verbal IQ is particularly compromised relatively to performance IQ (Bresolin et al., 1994; Cohen et al., 1968; Cotton et al., 2001; Florek & Karolak, 1977, Karagan, 1979).
More precisely, Emery & Muntoni (2003) found, in a cohort of DMD patients, that the overall mean intelligence quotient was 82, so approximately 1 SD below the population mean. 19% of the tested patients had an intelligence quotient below 70, that is the cut-off point for mental retardation.

The cognitive deficits more frequently observed in DMD patients are poor expressive verbal abilities, reduced short term memory, specific disabilities in learning to read, write and calculate, with relatively intact visuospatial cognitive abilities (Banihani et al., 2015; Billard et al., 1998; Cyrulnik et al., 2008; Hinton et al., 2000; Karagan et al., 1980; Mento et al., 2011).
Other Authors point out impairments in verbal working memory (Hinton et al., 2000) and phonological processing (Billard et al., 1992; Dorman et al., 1988) as the main source of difficulty in these patients' verbal processing. These deficits likely contribute to limited academic achievement.
DMD patients show significant lower performance relatively to peers also in tests assessing attention and EF (Anderson et al., 1998; Cotton et al., 1998; De Moura et al., 2010; Donders & Taneja, 2009; Mento et al., 2011; Wicksell et al., 2004; Wingeier et al., 2011). In particular, they fail in verbal fluency test, Trial Making Test and Tower of London test.

4.1.3. Personality Traits and Social Cognition

Considering the behavioral and personality traits that can characterize the patients affected by DMD, literature frequently reports experience of insecurity, behavioral immaturity and social inhibition, maybe as a consequence of the disease, as well as social withdrawal and reduced access to common activities (Hinton et al., 2006). Deficits in mental flexibility and emotional regulation could result in opposing and provocative behavior, as well as problems concerning explosive temperament (Bushby et al., 2009).

As regards differences between younger and older boy with DMD, significant dissimilarities were found in areas of recreational, social and skill-bases activities. In the study of Bendixen et al. (2014) older boys with DMD reported lower levels of participation in these areas, as well as less engagement in activities with individuals other than family members and less participation outside home. Moreover, significant decline in social activities and community based engagement as the boys with DMD age was evidenced.

On the other hand, Poysky (2007) reported that DMD children between 8 and 10 had significantly poorer total psychological adjustment scores compared to older boys affected by the disease. In general, total adjustment scores improved with age, suggesting that the boys became better adjusted as they grew older and became wheelchair-bound.

Many studies revealed that DMD patients show higher incidence of neuropsychiatric disorder, such as ADHD, ASD and Obsessive-Compulsive Disorder (OCD), compared to normal population (Joseph et al, 2008; Hendrikensen et al., 2006).
Moreover, almost 30-50% of DMD patients show social behavior problems or psychosocial problems (Hinton et al., 2006; Polakoff et al., 1998). Also depressive symptoms and anxiety are reported by DMD patients (Fitzpatrick et al., 1986).

Finally, considering DMD children treated with corticosteroids, it emerged that these patients can experience collateral negative psychological effects, even if literature highlights that steroids are not the main factor that contributes to behavioral problems in these patients (Hinton et al., 2006).

4.2. BECKER MUSCULAR DYSTROPHY

4.2.1. The disease

BMD is a disorder derived from the mutation of the gene of dystrophin protein which is product in partial or altered way.

BMD is strictly related to DMD because it is substantially the same disorder which involves the same muscle groups, but it shows a lesser degree of severity.

Both BMD and DMD are recessive diseases linked to the X chromosome that cause progressive muscle weakness in male subjects. However, in BMD patients the mutation allows for the expression of truncated but functional dystrophin or a reduced amount of dystrophin protein. In particular, in BMD muscles the expression of mutated dystrophin is observed with highly variable extent from less than 10% to as high as 75% of the full length expression of normal muscles (Neri et al., 2007; Antony et al., 2011).

The incidence of BMD is 1 in 18000 newborn males (Bushby et al., 1991) and the prevalence is around 2.4 per 100000 born male (Yilmaz et al., 2012).

BMD causes very heterogeneous clinical phenotypes: the age of onset is highly variable (from 2 to 45 years) and so the rate of progression of the disease and its severity: actually, some BMD patients are highly asymptomatic while other become wheelchair confined around 16 years old (Le Remeur, 2015).

The typical presentation of BMD consists in a juvenile onset muscle wasting and weakness, predominant at the thigh extensor and pelvic girdle, calf hypertrophy, with a gradual progression that leads to loss of motor function over years or decades, and frequent dilated cardiomyopathy, not proportional in severity to muscle involvement (Bello et al., 2016; Darras et al., 1993). Muscular weakness forces the patients to a wheelchair and then engage all muscle groups.

BMD patients may live until the fifth or sixth decade of life; cardiomyopathy represents the number one cause of death in these patients (Connuk et al., 2008) followed by pulmonary complications (Emery, 1993).

4.2.2. Cognitive Profile

In literature the studies concerning the cognitive abilities of BMD patients are really scarce and always secondary comparing to DMD investigation.

In general, existing reports indicate that BMD patients can manifest intellectual impairment and low verbal IQ, as well as psychiatric disturbances (Bradley et al., 1978; Bushby et al., 1993).

Considering the study performed by Young et al. (2008), that is one of the few that focus only on BMD patients, it emerged that 21% of the sample had difficulties with reading, 32% showed difficulties with spelling and 26% of the patients had problems with arithmetic. These frequencies are all significantly higher in comparison with healthy population.
Moreover, the study revealed also a higher incidence of learning difficulties relatively to controls.

Impairment of cognitive abilities in BMD patients, as well as in DMD patients, seems to be related to a dysfunction of Dp140 brain isoform (Bardoni et al., 1999).

4.2.3. Personality Traits and Social Cognition

As regards social functioning, Grootenhuis et al. (2007) revealed that the most physically compromised adult patients affected by BMD showed more obvious problems in social functioning level (Grootenhuis et al., 2007).
Indeed, the psychological stress due to physical involvement may contribute to the behavioral problems often detectable.
In aforementioned Young's study it have been shown a higher incidence, among BMD patients, of individuals with ASD relatively to healthy population (8.3%), while the frequency of total behavior problems in the clinical range was 67%.
The behavioral problems that can be present in BMD patients increase caregivers stress even more, creating a vicious circle (Nereo et al., 2003).

Considering problems that can influence negatively the behavior and the social functioning of BMD patients, Lager et al. (2015) reported that sixty-nine per cent of the BMD patients interviewed complained about pain during the past three months and 50% reported chronic pain.
The pain prevalence did not differ significantly between ambulators and non-ambulators patients and it typically occurred weekly, most frequently in the neck/back or legs.

The areas that were most affected by pain were general activity and mood, result confirmed also by Zebraki & Drotar research (2008).

Finally, a study of Eggers et al. (1998) compared BMD patients with patients affected by limb girdle muscular dystrophy (LGMD) and FSHD patients. BMD patients didn't show worse social adjustment in comparison with LGMD and FSHD patients, even if BMD patients had more physical problems relative to the other two sample of patients.
Unexpectedly, BMD patients showed higher emotional problems.

4.3. FACIOSCAPULOHUMERAL DYSTROPHY

4.3.1. The disease

FSHD is the third most common muscular dystrophy.
It's a dominantly inherited disorder that generally has a slow progression and causes muscular weakness, fatigue and inflammation in affected patients (Tawil et al., 2006; Wang and Tawil., 2016).

The disease typically develops from the second decade but it can begin also in infancy; the prevalence is about 1 case every 8.000-22.000 with wide regional differences (Wang et Tawil., 2016).

The molecular basis come from the aberrant expression of the DUX4 gene of 4q35 chromosome in skeletal muscle (Lemmers et al., 2010).
Preliminary evidences suggest that inappropriate expression of DUX4 gene, that lies in D4Z4 macrosatellite repeat, and its transcriptional targets in skeletal muscle can result in apoptosis, impaired muscle regeneration and induction of an immune response.

Whereas 95% of the patients affected by FSHD have contractions (from 1 to 10 repeat units) in the D4Z4 gene (FSHD1), the 5% of patients, clinically indistinguishable from FSHD1, have a number of D4Z4 repeats on the normal range. These patients, labeled FSHD2, carry mutations in genes on other chromosomes resulting in hypomethylization of D4Z4 gene on both copies of 4q35 chromosome (Wang and Tawil, 2016).

Even though the disease is frequently inherited, up to 30% of the cases are sporadic, arising from de novo mutation; female tend to be less severely affected than males (Tonini et al., 2004).

Typical symptoms that are evident in 70-85% of the patients are winged scapula, as well as facial, shoulder girdle, trunk and lower extremity weakness (Wang and Tawil, 2016). The disease can involve also pulmonary functioning in the 2-13% of the cases, it can cause cardiac arrhythmias (10%) and hearing loss (Kilmer et al., 1995).
About 20% of individuals affected by FSHD become wheelchair dependent after the fifth decade (Tawil et al., 2006).

Smaller D4Z4 repeat size is associated with more severe disease as measured by age at diagnosis, age at onset and age at wheelchair dependence (Lin et al., 2015; Statland et al., 2014).

The disease generally does not reduce life expectancy, but of course this depends on the possible involvement of the respiratory muscles or the presence or absence of severe arrhythmias (Richard et al., 1999).

Nowadays, FSHD has no effective treatments, although many drugs have been tried in several clinical trials, for example prednisone (Tawil et al., 1997), albuterol (Kissel et al., 2001), diltiazem (Elsheikh et al., 2007).

4.3.2. Cognitive profile

As regards the cognitive profile of FSHD patients, there are evidences that the disease can be associated to several CNS disorders, such as epilepsy, speech delay, and mental retardation (Grosso et al., 2011).
In particular, in FSHD patients there are reports of mild to moderate cognitive deficiency and possible epilepsy in an early-onset case of FSHD, often with associated deafness and retinopathy (Bindoff, 2006). Overt mental retardation has been described only in a child with a larger deletion defect (Hobson et al., 2006).

An interesting study of Sistiaga et al. (2009) found that patients affected by FSHD showed mild learning-level differences in the neuropsychological profile. In this study, patient's IQ was related to the size of deleted fragment but not to the degree of muscular impairment. FSHD patients could be divided in two distinct cognitive profile: patients with a EcoRI fragment size more than 24kb rarely showed cognitive impairment whereas patients with a EcoRI fragment size below 24kb showed a reduce IQ levels and difficulties in verbal functioning, visuo-constructive tasks and reduced learning capacity.

As regards neuroimaging findings, FSHD patients have significantly less gray matter relatively to healthy controls (Quarantelli et al., 2006). Moreover, it seems that gray matter loss displays a

borderline correlation with clinical severity, even if brain tissue volumes seem to not correlate with disease duration, size of the genetic deletion, age at onset.
In particular, clusters of gray matter loss are evident in the left precentral cortex, in the anterior cingulate and in the right fronto-polar region (Quarantelli et al., 2006).
Finally, it has been detected less intracortical inhibition in comparison with healthy population (Di Lazzaro et al., 2004).

4.3.3. Personality Traits and Social Cognition

A really debilitating problem that has a really large impact on participation, social contacts and the Quality of Life of FSHD patients is fatigue, that is described as an *overwhelming and unpredictable experience* (Schipper et al., 2016). Fatigue can be the result of weak muscles, physical overachieving or underachieving and stress. But most of the time FSHD patients do not know the actual causes of the fatigue, which makes it hard to deal with.

Also pain and imbalance are common in persons affected by FSHD (Smith et al., 2014).
The most severe symptoms regard fatigue and were most likely to stay the same or worsen since onset of the disease. Pain and imbalance seem to be associated with mental health, social integration and productive activity.
The study of Jensen et al. (2008) confirmed that up to 79% of patients with FSHD complained of pain. The most common sites of pain are the lower back, legs, shoulders and neck.

Considering disease burden, a study by Johnson et al. (2012) found that FSDH patients' affliction relatively to their illness was principally associated with mobility impairment, activity limitation, and social role limitation.

Fatigue, pain and disease burden can lead FSHD patients to manifest depressive symptoms. In fact, FSHD patient seems to show a predisposition for depressive disorders (Melo et al., 1995).

4.4. X-LINKED SPINAL AND BULBAR MUSCULAR ATROPHY (KENNEDY DISEASE)

4.4.1. The disease

X-SBMA, or Kennedy's Disease (KD), is an extremely rare neurological disorder caused by an expansion of the trinucleotide CAG repeat, which encodes the polyQ tract, in the first exon of the androgen receptor (AR) gene (Kennedy et al., 1968).

The abnormal number of repetitions of the trinucleotide CAG causes the increase of the sequence of glutamine within the AR. The expansion of the polyglutamines sequences (polyG) leads to insensitivity to androgens and neurodegeneration (Querin et al., 2015).
These AR aggregates have been implicated in the pathogenesis of X-SBMA in two different ways: loss of normal AR function, inducing neuronal degeneration, and the pathogenic AR acquiring toxic proprieties damaging motor neurons (Adachi et al., 2005).

In healthy individuals, the number of CAG repeats ranges from 10 to 36, whereas patients affected by X-SBMA have between 40 and 68 repeats (Grunseich et al., 2014; Parodi & Pennuto, 2011). Moreover, the age of onset correlates with CAG-repeat length (Atsuta et al., 2006; Fratta et al., 2014).
The number of CAG repeats is not constant in every cell of an individual, but its number may vary across tissues (Nihei et al., 2013), and this instability is known as *somatic mosaicism* (Tanaka et al., 1999).

Among the hereditary motor neuron diseases, X-SBMA has one of the lowest prevalence, with a figure of 3.3/100,000 among the male population, although it is thought to be a largely under-diagnosed condition (Guidetti et al., 2001). Females carrying the elongated CAG repeat are usually not symptomatic or express subclinical manifestations of the disease (Mariotti et al., 2000).
First symptoms of X-SBMA usually appears between 30 and 50 years (Katsuno et al., 2012).

Clinical features of X-SBMA have classically been described as caused by neuronal and non-neuronal deficits (Jokela et al., 2016), both depending on patients' androgen insensitivity (Warner et al.,

1992). Neuronal deficits manifest at a muscular level as limb weakness, cramps, dysphagia and nasal speech (Sorarù et al., 2008). Frequently, patients present with perioral or postural tremor (Atsuta et al., 2006; Rhodes et al., 2009). Further symptoms may be proximal or distal flaccid weakness, dysarthria, hanging jaw (jaw drop) and fasciculations (Jordan & Lieberman, 2008; Larsen & Smith, 2005).
In the majority of cases weakness first affects the lower limbs, followed by the upper limbs, the bulbar muscles, and lastly the facial muscles (Atsuta et al., 2006).

Non-neuronal symptoms are displayed as gynecomastia, testicular atrophy and decreased fertility (La Spada, 2014).

X-SBMA progresses slowly to the end stage with a median duration from onset assessed by muscle weakness to death of 22 years. The most common cause of death seems to be pneumonia and respiratory failure (Atsuta et al., 2006).

4.4.2. Cognitive profile

The extensive accumulation of mutant androgen receptors, that lead to physical degeneration, have also been observed in non-cortical areas of the brain (Adachi et al., 2005).
This finding is extremely important, because sexual hormones have a strong impact on neurodevelopment and cognition (Lombardo et al., 2012; Auyeung et al, 2013).

At a neuropathological and histopathological level, some Authors have observed alterations mostly in frontal sites, but also in limbic areas and in the brainstem, affecting both grey and white matter.
In detail, Kassubek et al. (2007) highlighted extensive white matter atrophy in frontal areas, subcortical areas, cerebellum and dorsal brainstem in X-SBMA patients.
White matter degeneration in the corticospinal tract and in the limbic system was found in these patients by Unrath et al. (2010), while the study of Pieper et al. (2013) described white matter degeneration mainly in the brainstem and the cerebellum and widespread changes in central white matter tracts.
Glucose metabolism has been studied and a reduced activity has been uncovered in frontal areas of the cerebrum (Lai et al., 2013).

Finally, a recent magnetic resonance investigation on a heterogeneous sample of motor neuron disease patients revealed cortical thinning in frontotemporal, insular and motor regions and white matter damage to motor callosal fibers (Agosta et al., 2016).

Several single-case studies assessing cognitive abilities of X-SBMA patients have been carried out, because of to the rarity of the disease.

The study of Mirowska-Guzel et al. (2009), involving a 53-year-old man affected by X-SBMA, revealed in this patient mild impairment in visual short-term memory, visuospatial and visuoconstructive abilities. His personality was altered as well, experiencing fatigue, anxiety, irritability and apathy that led to altered social conduct. The Authors concluded that the altered state might be part of this disease.

Another single-case has been reported by Kessler et coll. (2005) and involved a 48-year-old X-SBMA patient with clinical features of FTD, a common feature in the wide family of motor neuron diseases.

As regards the study of samples of X-SBMA patients, the first attempt was performed by Guidetti et al. (1996), who assessed the neuropsychological functioning of 19 male and female members of a large family, with five of them presenting X-SBMA. Guidetti found neuropsychological impairment in some carriers and in all symptomatic patients as regards attention, EFs and verbal memory.

Of particular interest is the work by Soukup et coll. (2009), who extensively investigated the neuropsychological abilities of 20 X-SBMA patients. This study demonstrated that X-SBMA patients had deficits in short and long term memory, as well as working memory, verbal and non-verbal fluency, even if at subclinical level.

Contrasting results were found in another study (Kasper et al., 2014), where short and long term memory of X-SBMA patients were spared when compared with healthy controls. EFs had minimal deficits, as well as attention.

A Chinese sample of 10 patients (Yang et al., 2014) underperformed, relative to 12 healthy controls, in almost all of the tests administered during the assessment. It should be noted that both patients and controls had a score in the Montreal cognitive assessment (MoCA) well under the mild cognitive impairment cut-off (means of 17.1 and 23.0 for patients and controls, respectively).

Definitely different results were found in the study of di Rosa et al. (2015), in which 20 X-SBMA patients were compared to healthy controls on aspects regarding the neuropsychological assessment and empathic abilities. Subjects were tested through digit span, story recall, TMT and phonemic fluency tests. No significant differences were found between the two groups. The conclusion was that patients were not impaired in their general cognitive functioning, relative to controls. On the contrary, from di Rosa study emerged a non-significant trend relatively to a better performance of X-SBMA patients on the Babcock story recall test, if compared to the control group.

All the studies reported above correlated the cognitive capacities with the physical measures of the patients. No reliable connections were found between neuropsychological scores and disease duration or indexes of severity, nor with CAG repeat length. Despite the results emerged, these correlations seem worth to be measured because in ALS correlations have recently been found between a standardized neuropsychological battery and measures of physical impairment (Osborne et al., 2014).

4.4.3. Personality Traits and Social Cognition

X-SBMA patients don't seem to exhibit particular behavioral diseases, neither a higher incidence relative to these pathologies, relatively to healthy population (Rhodes et a., 2009).

However, from a clinical viewpoint, it's common for these patients to show particular psychological characteristics such as diffidence, marked emotional sensitivity and concentration problems. The picture presented by these observations seems to confirm that higher-order frontotemporal functions could be particularly vulnerable in X-SBMA patients, as often seen in ALS (Phukan et al., 2007).

Shaw et al. (1998) described two X-SBMA patients, with only one of them who had an altered personality, being less considerate and easily irritable. Interestingly, only the patient with the altered personality showed histopathological changes in the prefrontal cortex and hippocampus, with neuronal depletion and gliosis.

The study of Di Rosa et al. (2015) aforementioned focused also on Empathic abilities of X-SBMA patients.

Authors found a clear dissociation between Cognitive and Affective Empathy in X-SBMA patients, as measured by the Faux Pas Test and the Reading the Mind in the Eyes Test.

In particular, X-SBMA patients showed distinctive deficits in Cognitive Empathy, whilst Affective Empathy appeared to be preserved.

This was the first evidence of a higher-order dysfunction, different from the already studied executive domain. Results suggest that the disease can impact fine-grained abilities, such as ToM.

5. PRELIMINARY HYPOTHESES

5.1. Duchenne muscular dystrophy

DMD patients lack of dystrophin protein (Anderson et al., 2002) and this is associated to cognitive deficit in one third of DMD patients (D'Angelo et al., 2006). The cognitive impairment described in these patients regards also EFs (Anderson et al., 1998; Donders & Taneja, 2009; Mento et al., 2011).

Considering behavioral peculiarities, DMD patients show higher incidence of neuropsychiatric disorders, such as ADHD, ASD and OCD, compared to normal population (Joseph et al, 2008; Hendrikensen et al., 2006), almost half of DMD patients show social behavioral problems or psychosocial problems (Hinton et al., 2006; Polakoff et al., 1998). Depressive symptoms and anxiety are often reported by DMD patients (Fitzpatrick et al., 1986).

As regards dystrophin mutation, it has been demonstrated that DMD patients with mutations located in the distal portion of the dystrophin gene are generally more severely affected relatively to DMD patients with proximal mutations (D'Angelo et al., 2011).

The relation between EFs and ToM is well established, considering that the development of ToM is related to the integrity of EFs (Russell, 1997; Carlson et al., 2002) and that the neural correlates of ToM and EFs are partially overlapping, (Eslinger, 1998; Shamay-Tsoory, 2003; Hansel et al., 2008; Carter et al., 1998; Zaki & Ochsner, 2012).

Considering all these evidences, we expected a worse performance of DMD patients relative to healthy controls on EFs tests. Moreover, we foresaw a worse performance of DMD children also in Empathy tasks, in particular in those assessing ToM.

Focusing on the link existing between EF and ToM, we expected a correlation between the tests assessing ToM abilities and the tasks related to EF; on the other hand, no correlation between EFs and the task assessing Affective Empathy was contemplated.

It seemed interesting to investigate, in the two samples, the types of emotion errors made in the Affect Recognition test; in particular, we tried to understand if the types of errors were significantly different in the two samples.

Finally, considering the relation between dystrophin mutations and cognitive abilities, we expected that DMD patients with distal mutations would perform worse relatively to DMD patients carrying proximal mutations on the neuropsychological evaluation.

5.2. Becker muscular dystrophy

BMD is strictly related to DMD. although the mutation present in BMD patients allows for the expression of truncated but functional dystrophin (Neri et al., 2007).

As regards cognitive functioning, BMD patients can manifest intellectual impairment, low verbal IQ, difficulties in reading, spelling and arithmetic (Bradley et al., 1978; Young et al., 2008).

Considering behavioral peculiarities, among BMD patients has been found higher incidence of individuals with ASD and total behavior problems, relatively to healthy population, as well as psychiatric disturbances (Bushby et al., 1993; Young et al., 2008).

Cognitive impairment in BMD patients seems to be related to a dysfunction of Dp140 brain isoform, as shown in DMD patients (Bardoni et al., 1999).

Considering all the evidences related to this disease, we expected from BMD patients a performance on the EFs tests and ToM tasks statistically comparable to the performance of the control group but slightly worse at a subclinical level. On the other hand, we foresaw that the performance on Affective Empathy tests would be statistically comparable to the performance of the control group.

As discussed for DMD, also in BMD patients we expected a correlation between the tests assessing ToM abilities and the tasks related to EF; on the other hand, no correlation between EFs and the tasks assessing Affective Empathy was contemplated.

Finally, considering the relation between dystrophin mutations and cognitive abilities, we expected that BMD patients with distal mutations would perform worse on the neuropsychological evaluation relatively to BMD patients carrying proximal mutations.

5.3. Facioscapulohumeral dystrophy

FSHD is a disease that primarily causes muscular weakness (Wang and Tawil., 2016) but there also evidences regarding CNS involvement and associated disorders, such as epilepsy, speech delay and mental retardation (Grosso et al., 2011).

Cognitive profile of FSHD patients seems to be related to EcoRI fragment size: patients with a EcoRI fragment size below 24kb shows reduce IQ levels and difficulties in verbal functioning, visuo-constructive tasks and reduced learning capacity (Sistiaga et al., 2009).

As regards neuroimaging findings, FSHD patients show gray matter loss in the left precentral cortex, anterior cingulate and in the right fronto-polar region (Quarantelli, 2006) and less intracortical inhibition, in comparison with healthy population (Di Lazzaro et al., 2004). It's important to note that the anterior cingulate cortex is a region implicated both in Affective Empathy tasks and in Cognitive Empathy performance (Vollm et al., 2006).

Considering the evidences just described, we expected a slightly worse performance of FSHD patients, relatively to the control sample, in EFs tests and ToM tasks and, on the other hand, no differences between the two samples on Affective Empathy evaluation.

Moreover, it has been investigated the presence of correlations between EF tasks and ToM tests in FSHD patients.

Finally, we expected that FSHD patients with an EcoRI fragment size below 24Kb would perform worse in neuropsychological assessment comparing to FSHD patients with a fragment size over 24Kb.

5.4. X-Linked Spinal and Bulbar Muscular Dystrophy

X-SBMA is caused by an expansion of the polyglutamines sequences that leads to gene insensitivity to androgens (Kennedy et al., 1968). The extensive accumulation of mutant androgen receptors, that causes physical degeneration, has also been observed in non-cortical areas of the brain (Adachi et al., 2005).

Contrasting results regarding the cognitive performance of SBMA patients emerge from literature: some Authors have found cognitive impairment in these patients, in particular in tests assessing EF (Guidetti et al., 1996; Soukup et al., 2009), while other Authors didn't find deficits after neuropsychological assessments (Kasper et al., 2014; di Rosa et al., 2015).
The problem related to all these studies is the small size of the samples, which were composed by a maximum of 20 patients.

Of particular interest is the finding relative to di Rosa study (2015) in which SBMA patients showed a better performance on Babcock story recall test relatively to healthy controls, even if at a subclinical level.

In the light of the evidences presented, it has been carried out an explorative study with the aim to evaluate the EFs of SBMA patients considering larger samples of SBMA patients and controls. In particular, we expected a better performance of SBMA patients, relative to controls, only on the Babcock story recall test, even if at a subclinical level.

Furthermore, we investigated the relationship between cognitive performance and physical assessment tests in order to highlight any relation between the performance at the neuropsychological test and the physical impairment, hypothesizing a negative correlation between neurological measures and cognitive abilities.

Finally, it has been hypothesized that the degree of expansion of poliQ and the testosterone levels would predict the outcome in the neuropsychological evaluation, considering the impact that testosterone may have during the course of cognitive assessment (Lombardo et al., 2012).

6. METHODS

6.1. DUCHENNE MUSCULAR DYSTROPHY

6.1.1. Participants

The participants of this study were 25 male children affected by DMD (mean age: 10.22; SD: 2.9) and 25 healthy controls (mean age: 10.2; SD: 3) matched for age and gender.

DMD patients had a genetically diagnosed DMD and referred to the Motor Neuron Disease Centre of the Padua University Hospital, while healthy controls were volunteers recruited by posting flyers unrelated to DMD patients but with the same age and gender.

Exclusion criteria regarded the presence of overt and certified cognitive deficit, the occurrence of psychiatric problems or the presence of other neurological diseases. For this reason, before the enrolment of the children for the study, we verified the presence of any of these problems in their medical records and we asked confirmation to their caregivers.

Moreover, only patients with an age between 3 and 16 years old were eligible for this study; this was because of the instruments used for the neuropsychological assessment. The children enrolled belonged to different nationalities, but everyone spoke and properly read the Italian language.

All caregivers signed an informed consent, approved by the ethical committee of the University of Padua, in line with the declaration of Helsinki. Adolescents signed an informed assent too.

For DMD children, the neuropsychological evaluation was administered after having completed the neurological examination.

Subjects completed the evaluation with the psychologist while caregivers waited in a next room; the protocol lasted about one hour.

6.1.2. Neuropsychological Assessment

For the assessment of cognitive and empathic profile of DMD patients and heathy controls it has been used a developmental neuropsychological battery, the NEPSY II (Korkman et al., 2007). NEPSY II is an internationally recognize measure for neuropsychological assessment designed specifically for children and adolescents (Korkman et al., 2007; Korkman, Lahti-Nuuttila et al., 2013; Narzisi et al., 2013; Olivieri et al., 2011; Pirila et al., 2004). This instrument was developed following the

neuropsychological approach of Luria (1962), who considered multiple brain system at the base of cognitive functioning; it provides a comprehensive overview of the child's neuropsychological functioning.

In this research we used the Italian Version of NEPSY II (Korkmann et al., 2007; Urgesi et al., 2011). The battery is composed by 33 subtests divided into 6 cognitive domains: Attention and Executive Functions, Language, Memory and Learning, Sensorimotor Functions, Social Perception and Visuospatial Processing.
It was administered both the version for 3-4 years old children and the form created for 5-16 years old children/teenagers. Some tests can be submitted to all age groups, whereas others are age specific.

In this study it has been proposed to children only two domains of the battery: Executive Functions and Social Perception. It has been made this choice firstly because the aim of this study was to evaluate the functioning and the relation between EFs and Empathy, so the evaluation of other domains would be interesting but not strictly related to the purpose of our research. Secondly, DMD children were evaluated when they were in Motor Neuron Disease Centre of the Padua University Hospital and after completing the neurological evaluation, so it has been created a protocol that was not too long for the child (the administration takes approximately one hour) and that did not require that the child and his family to come back to the Hospital another time to complete it (most of the children live far away, it would be stressing for them and for their parents to return again in a short time).

As regards the domain Attention and Executive Functions, the subtests proposed were Inhibition, Clock, Statue and Animal Sorting. Considering the domain Social Perception, the two subtests that constitute this section are Theory of Mind and Affect Recognition.

Here a brief description of all the subtests used:

- Inhibition evaluates the ability to inhibit automatic responses and shift between congruent responses during naming of visual stimuli. The Naming condition (A) requires to name the shape of squares and circles or the up or down direction of the arrows; the Inhibition condition (B) requires to provide the opposite naming response on the same stimuli; the Switching condition (C) requires to provide the congruent or incongruent naming response according to the color of the stimulus. This test can be conducted by children between 5 and

16 years old and results in 6 different scores: 3 scores indicate the time needed to the subject to complete the subtest (Inhibition_A_time, Inhibition_B_time, Inhibition_C_time) while the other 3 scores refer to the combination of the time needed to complete the subtest and the errors made (Inhibition_A_Combi, Inhibition_B_Combi, Inhibition_C_Combi).

- Clocks test evaluates planning and organization of visuospatial perception and responses and the concept of time by requiring to read or draw the times in analogical or digital clocks. The task can be completed only by children older than 7 years old.
- Animal Sorting test requires to sort eight cards into two groups of four cards each using various self-initiated sorting criteria and can be proposed only to children older than 7 years old.
- Statue test assesses inhibition of impulses. The child is required to stand and keep his eyes closed and stay still for 75 seconds, despite the examiner's attempts to distract him, for example by knocking on the table or coughing. The test has been created for children between 3 and 6 years old.
- Theory of Mind test is one of the two subtests of Social Perception. The test assesses the ability to understand mental functions such as belief, intention, deception, emotion, imagination and pretending, as well as the ability to understand that others have their own thoughts and feelings. Furthermore, it evaluates the capacity to understand how certain emotions are linked to given social situations.

  The test is composed by a Verbal part in which participants are provided with verbal or pictorial descriptions of some social situations and are, then, asked questions about those situations which require the understanding of the characters' point of view. On the other hand, the Contextual part evaluates the capacity to understand how certain emotions are linked to given social situations and to recognize correctly the emotions that the various social settings generate (Appendix I).
- Affect Recognition task assesses the ability to recognize emotional expression, so happiness, sadness, anger, fear, disgust and neutral, from photographs of children's faces in four different tasks. Participants need to match the two faces expressing the same emotion among three or more alternatives. The test is composed by four parts: children younger than 5 can complete only the first and the second part, children between 5 and 6 years can complete also the third part (Appendix II).

In addition to these tests, it was administered to the samples another test assessing EFs: The Modified Card Sorting Test (MCST), a shortened version of the Wisconsin Card Sorting Test, proposed by Nelson in 1976. The Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948) evaluates abstract reasoning, mental flexibility and problem solving skills. The individuals are required to generate, test, modify and select hypotheses to discover a sorting principle that changes surreptitiously. The original version of WCST includes 128 cards, it could take a long time to complete, for some patients results too difficult and includes some ambiguous stimuli that could be classified according to more category. The version proposed by Nelson, however, is composed only by 48 items and doesn't include ambiguous items. Four principal scores have been considered for MCST: the number of categories completed, the number of correct answers, the number of errors made and the number of perseverative errors committed.

6.1.3. Neurological Evidences and Dystrophin Mutation

In DMD sample, we considered loss of ambulation, cardiomyopathy and the assumption of cortisone therapy. Four patients presented loss of ambulation, two patients suffered of cardiomyopathy and twenty-three patients assumed cortisone therapy.

It wasn't considered the presence of slowdown in motor activity of the upper limbs because the patients evaluated were all able to write and draw without significant problems and because the tasks administered, even timed one, were not related specifically to the speed of upper limbs movements.

Moreover, we considered the type of mutation in the dystrophin gene. In particular, we distinguished between patients bringing distal mutations in the intron 44 of dystrophin gene and patients with proximal mutations relative to intron 44. This type of partition was done because, as explained in chapter four, DMD patients with mutations located in the distal portion of the dystrophin gene, so involving the Dp140 brain protein isoform, were generally more severely affected and expressed different patterns of strength and cognitive impairments relatively to DMD patients with mutations located in the proximal portion of the dystrophin gene, not involving Dp140 (D'Angelo et al., 2011).

6.2. BECKER MUSCULAR DYSTROPHY and FACIOSCAPULOHUMERAL DYSTROPHY

6.2.1. Participants

Patients affected by BMD and FSHD underwent the same research protocol.

The participants were 21 male affected by BMD, together with 21 controls matched for age (BMD mean age: 39,1; SD: 12,9. Controls mean age: 38,5; SD: 12,6), education (BMD mean education: 11,5; SD: 3,1. Controls mean education: 11,6; SD: 2,7) and gender.

Moreover, there were 21 patients affected by FSHD and 21 healthy controls matched for age (FSHD mean age: 50,6; SD: 16,2. Controls mean age: 49,8; SD: 16), education (FSHD mean education: 12,7; SD: 4,4. Controls mean education: 12,6; SD: 4,2) and gender as well. Control group participants were volunteers recruited by posting flyers.

These patients had a genetically diagnosis of BMD or FSHD and referred to the Motor Neuron Disease Centre of the Padua University Hospital. Exclusion criteria regarded the presence of cognitive impairment, the occurrence of psychiatric problems or evidences of other neurological diseases. Moreover, only patients older than eighteen years old were eligible for this study; this was because of the instruments used for the neuropsychological assessment.

All participants signed an informed consent, approved by the ethical committee of the University of Padua, in line with the declaration of Helsinki.

For BMD and FSHD patients, the neuropsychological evaluation was administered after having completed the neurological examination. The participants completed the evaluation with the psychologist; the protocol lasted about one hour and half.

6.2.2. Neuropsychological Assessment

The evaluation of both patients and healthy controls was composed by two parts: the assessment of EFs, which included the administration of five tests, and the evaluation of Empathic abilities, conducted using two tests and two questionnaires.

Here a brief description of all the tools used:

Executive Functions

- Digit Span Forward (DS_f; Spinnler & Tognoni, 1987): in DS_f test the subject has to memorize increasing series of numbers. This is a measure of Short-Term Memory capacity, the phonological loop in Baddeley's theory (1986).
- Digit Span Backward (DS_b; Spinnler & Tognoni, 1987); the participant has to repeat the numbers read by the examiner in the reverse order. DS_b is a measure of Working Memory that requires maintaining the items but also mentally manipulating them engaging resources of the Central Executive (Baddeley, 2010).
- Trial Making Test (TMT; Reitan, 1958): the TMT test assesses attentional abilities in a standard condition and in a switching condition. In TMT A subtest, the subject has to join with a line the numbers from 1 to 25 in the shortest time possible while in TMT B subtest the participant has to join with a line numbers and letters, alternating the two different kind of symbols and following both the number order and the alphabetical order. The scores indicate the time needed to complete the tasks and the score used in the statistical analysis of this research was the subtraction of TMT B - TMT A that is the most relevant one.
- Phonemic Fluency Test (FAS; Benton, 1968; Novelli et al., 1986); this test is an important measure of the ability to categorize words in an unfamiliar way. The subject has to say as many words as possible starting with a given letter of the alphabet. The score used is relative to the sum of all the words produced by the participant.
- Modified Cart Sorting Test (MCST; Nelson, 1976): The MCST is a shortened version of the Wisconsin Card Sorting Test, proposed by Nelson in 1976. The Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948) evaluate abstract reasoning, mental flexibility and problem solving skills. MCST has been proposed also to DMD children but the type of correction made on raw scores changes between adults and children. The principal scores relative to MCST test are the number of category completed and the number of perseverative errors made.

Empathy Abilities

- Faux Pas test (FPt; Stone, 1998); The FPt is a verbal task that is classically described as a mainly cognitive measure of Empathy. In detail, in the FPt participants listen to 20 stories: 10 stories describe a faux pas, an embarrassing social mistake, and 10 control stories describe a minor conflict with no faux pas involved. The text of the stories is placed in front of the participant to reduce the demands on Working Memory. After the examiner has read each story, participants are asked: ‘‘Did someone say something wrong or inappropriate?’’ To understand whether or not a faux pas has occurred, participants need to imagine the mental state of the person who committed the faux pas and the person who might feel hurt or insulted. If a faux pas is identified, clarifying questions are asked. In all the stories, whatever the participants’ answer to the first question, memory questions are asked to assess their comprehension of the story. Following the original Authors’ indications, four separate scores are computed: one for faux pas-related questions on the faux pas stories (0 to 6), one for control questions on the faux pas stories (O to 2) one for faux pas-related questions on the control stories (0 to 2); and one for control questions on the control stories (0 to 2). Scores are given as the percentage of correct answers (Appendices III and IV).
- Reading the Mind in The Eyes test (RMET; Baron-Cohen et al., 2001): the RMET is a non-verbal task that typically reflects the affective and instinctive aspects of empathy, closely associated with the concept of ‘‘affective mentalizing” (Baron-Cohen et al., 2001). It’s a measure of the unconsciousness, in particular of the automatic and rapid processes of decoding mental states (Bodden et al., 2010; Kidd & Castano, 2013). This test consists of photographs of the eye region of 36 faces and participants are asked to choose one of four words printed below the photographs that best fit the feeling or thinking of the person in the picture. Participants score 1 point for each correctly answered photograph and corrected score is given as the percentage of correct answers (Appendix V).
- Interpersonal Reactivity Index (IRI; Davis, 1980): IRI is a self-report questionnaire with the aim to investigate Affective as well as Cognitive Empathy. This questionnaire is formed by 28 items, divided in 4 subscales: Perspective Taking, Fantasy Scale, Empathic Concern and Personal Distress. Perspective Taking (PT), which is the tendency to spontaneously adopt the psychological point of view of others, and Fantasy Scale (FS), tapping respondents' tendencies to transpose themselves imaginatively into the feelings and actions of fictitious characters in books, movies, and plays, are the two subscales used for scoring the cognitive

component of Empathy. On the other hand, Personal Distress (PD), measuring "self-oriented" feelings of personal anxiety and unease in tense interpersonal settings, and Empathic Concern (EC), assessing "other-oriented" feelings of sympathy and concern for unfortunate others, are the two subscales assessing affective empathy (Davis & American Psychological Association, 1980) (Appendix VI);

- Empathy Quotient (EQ; Baron-Cohen & Wheelwright, 2004): Empathy Quotient is a questionnaire that contains 40 Empathy items and 20 control items. Even if EQ was not designed to discriminate between Cognitive and Affective Empathy, this assessment tool has its roots in the cognitive approach of Empathy, known as ToM (Baron-Cohen & Wheelwright, 2004). Therefore, it's reasonable to state that this questionnaire explores Empathy from its cognitive point of view (Appendix VII).

6.2.3. Neurological Evidences

Considering BMD patients, it has been taken into account the presence or absence of cardiological disorders, evidences of respiratory failure and the age in which patients lost ambulation. None of the patients evaluated were wheel chaired, had cardiological problems or respiratory difficulties.
Moreover, we considered the type of dystrophin mutation present, as it has been done for DMD patients. So, BMD paticipants were distinguished between those carrying distal mutations and patients with proximal mutations relatively to intron 44.

As regards FSHD patients, considering the study of Sistiaga et al. (2009) aforementioned, we distinguished between patients with a EcoRI fragment size more than 24kb and patients with a EcoRI fragment size below 24kb, because of the relationship existing between the size of the fragment and cognitive performance.
Considering FSHD patients, none of the subjects evaluated were wheel chaired, had cardiological problems or respiratory difficulties.

6.3. X-LINKED SPINAL and BULBAR MUSCULAR ATROPHY

6.3.1. Participants

The participants were 70 male affected by X-SBMA and 78 healthy controls matched for age (SBMA mean age: 56,9; SD: 10,8. Controls mean age: 56,2; SD: 14,1), education (SBMA mean education: 11,1; SD: 4,2. Controls mean education: 11,1; SD: 4,2) and gender.

SBMA patients had a genetically diagnosis of X-SBMA and referred to the Motor Neuron Disease Centre of the Padua University Hospital while control group participants were volunteers recruited by posting flyers.

Exclusion criteria regarded the presence of cognitive impairment, the occurrence of psychiatric problems or evidence of other neurological diseases.

Moreover, only patients older than eighteen years old were eligible for this study; this was because of the instruments used for the neuropsychological assessment.

All participants signed an informed consent, approved by the ethical committee of the University of Padua, in line with the declaration of Helsinki.

For SBMA patients, the neuropsychological evaluation was administered after having completed the neurological examination. The participants completed the evaluation with the psychologist; the protocol lasted about forty-five minutes.

6.3.2. Neuropsychological assessment

Three of the tools used for the Neuropsychological evaluation of SBMA patients have already been described in the section “neuropsychological assessment” of BMD and FSHD patients.

In particular, the tests are the DS_f and DS_b (Spinnler and Tognoni, 1987), the FAS (Benton, 1968; Novelli, 1986) and the TMT (Reitan, 1958).

Moreover, it has been proposed the Babcock Story immediate and delayed recall test (Prose; Babcock, 1930; Spinnler and Tognoni, 1987), with the aim to repeat the same neuropsychological tests proposed in di Rosa study (2015).

The Babcock Story Immediate and Delayed Recall Test consists in a 21-unit story that is read by the examiner to the participant tested. Immediately following the first reading, the subject is asked to

recall everything he/she remembers about the story. After the first recall trial, the examiner read again the story and the recall following the second reading comes after approximately 10 minutes of testing involving nonverbal material. The score taken into account in this research comes from the sum of the two scores obtained during the immediate and the delayed recall.
The peculiarity of this test is that the story has an emotional content; in fact, it consists in an invented newspaper article that talks about a flood that caused dead, injured and sick (Appendix VIII).

6.3.3. Neurological measures

X-SBMA patients underwent neurological evaluation including six-minute walking test (6MWT; McDonald et al., 2010), task with the aim to evaluate ambulatory skills of patients affected by muscular dystrophies, and ALS functional rating scale (ALSFRS-r; The ALS CNTF treatment study, 1996), a useful instrument for the evaluation of functional status and functional change in patients affected by ALS and, more in general, by muscular dystrophies.

Moreover, in X-SBMA patients, testosterone levels and the number of expansions of PoliQ triplets were measured, considering their relation with cognitive performance.

6.4. STATISTICAL ANALYSIS

For DMD patients and control group, raw scores for each NEPSY-II subtest proposed were expressed as standardized scores (mean 10; SD 3) with respect to the age-matched normative sample values (Urgesi et al., 2011). For missing data, casewise deletion was applied.
Standardized scores used in the NEPSY-II (Korkman et al., 2007) range from 1 to 19, thus describing observed performance that is comprised within ±3 SD from the expected mean.
The results on the Clocks test, expressed with percentile scores, have been transformed in a seven-point ordinal scale, considering the categories in which the corrected scores were expressed by NEPSY-II while MCST raw scores were expressed as percentile scores.
The raw scores of emotions errors relatively to the Affective Recognition task have not been transformed in standardized scores because of the ambiguity that this conversion causes. In fact, using standardization, both particularly bad and particularly good scores are both converted in a low percentage, so that is impossible to distinguish them.

Considering the neuropsychological examination of BMD and FSHD patients, raw scores were used relatively to the DS_f and DS_b test, the FAS and the TMT, while MCST raw scores were expressed as percentile scores.
As regards the tests assessing empathic abilities, percentage scores have been used, as suggested by the Authors.

Non parametric Mann-Whitney U tests were performed to determine if there were statistically significant differences between patients and control participants in EF and Empathic abilities.
Spearman's rank correlation coefficient was used to assess the correlations between EFs and Empathy tasks, as well as relations between dystrophin mutation/size of EcoRI fragment and cognitive performance.
Non-parametric statistical methods were preferred because they require few, if any, assumptions about the shapes of the underlying population distributions and they are more robust for small samples (Kitchen, 2009; Siegel & Castellan, 1988).
Univariate ANCOVA was performed for each emotions errors of Affective Recognition test to explore between-group differences. In this analysis age and group were used as covariates.

As regards SBMA patients and their control group, both significantly large samples, and considering group comparisons, age and education levels were screened for violations associated with univariate tests, namely normal distribution (by using the Kolmogorov-Smirnov test) and homogeneity of variances (by using the Levene test).

Considering the clinical assessment, univariate ANCOVAs were performed to determine a statistically significant difference between patients and control participants on the neuropsychological tests administered.

Multiple linear regressions were performed to investigate the hypothesized relationship between genetic expression and testosterone and patient's cognitive performance. In both analyses, in respect of the count nature of DS_f and DS_b scores, Poisson regressions were employed to estimate such models. Logarithmic transformation was applied to TMT scores in order to assess their strong skewedness.

All analyses used age and education as covariates, as there is some evidence that educational level and aging can influence performance on similar tasks (Casals-Coll et al., 2013; Piatt et al., 1999; Ramsay et al., 1999; Stokholm et al., 2013; Woods et al., 2005).

Finally, Pearson correlation coefficients were employed to investigate the association between cognitive performance and measures of physical impairment (ALS-FRS and 6MWT).

For all analyses, two-tailed p values of less than 0.05 were considered significant.

Analyses were carried out using R software version 3.3.1.

7. RESULTS

7.1. DUCHENNE MUSCULAR DYSTROPHY

DMD and Control group on Executive Functions evaluation

From data analysis it emerged that DMD patients performed significantly poorer than control subjects in most of the EF tests administered, as it can be seen from Table 1.

Table 1: DMD patients and healthy controls on Executive Functions assessment

NEPSY II test	DMD					CONTROLS						
	n	M	SD	min	max	*n*	M	SD	min	max	p-value	
Inhibition_A_time	24	5,5	4,3	1	14	25	10,0	2,4	5	14	0,0003	***
Inhibition_B_time	24	6,5	3,8	1	15	25	10,6	2,3	7	14	0,0002	***
Inhibition_C_time	18	6,8	3,7	1	13	21	11,1	2,3	6	15	0,0004	***
Inhibition_A_Combi	24	8,5	3,0	2	14	25	10,3	2,7	6	15	0,08	
Inhibition_B_Combi	24	8,0	3,0	1	12	25	10,6	2,6	4	15	0,003	**
Inhibition_C_Combi	18	7,2	2,9	2	12	21	9,3	3,0	4	16	0.043	*
Animal Sorting	23	8,1	3,5	1	17	23	11,7	2,9	7	17	0,0005	***
Statue	4	9,0	2,5	7	12	2	11,0	1,4	10	12	0,46	
Clocks	19	2,7	1,8	1	6	23	4,9	1,2	3	7	0,0003	***
MCST_category	19	42,9	17,6	5	70	25	49,0	19,8	0	85	0,21	
MCST_correct answers	19	54,5	24,9	10	90	25	49,6	30,9	0	95	0,77	
MCST_errors	19	37,9	25,1	5	85	25	14,5	14,5	0	35	0,0009	***
MCST perseverative errors	19	19,2	22,8	5	95	25	7,2	6,0	0	20	0,02	*

Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

The scores in which DMD performance was comparable with the one of healthy controls were only three: the combined score of inhibition test - subtest denomination, the score relative to the statue test and the number of category completed on the MCST.

On the other hand, there was a statistically important difference between the performances of the two samples on all the three scores of the Inhibition test relative to the time required to complete the task (A: p= 0.0003; B: p= 0.0002; C: p= 0.0004), on the Animal Sorting test (p= 0.0005), the Clocks test (p= 0.0003) and the Errors made on the MCST (p= 0.009).

Moreover, DMD performance was under the cut-off of normality in all the scores relative Time of Inhibition task (A. M= 5,54; B. M= 6.5; C. M= 6.83).
Results are illustrated in Boxplot 1.

DMD and Control group on Empathy tasks

As regards the performance of DMD patients and healthy subjects on the ToM test, assessing Cognitive Empathy abilities, and the Affect Recognition test, assessing affective skills, it resulted that there was a significant difference between the two samples in both Cognitive and Affective Empathy test.

In particular, DMD performance resulted to be worse relatively to the performance of the control group in both ToM task (p= 0.005) and Affect Recognition test (p= 0.01).
Moreover, DMD performed more than 1 SD below normal range (mean=10; SD =3), as it can be seen in Table 2.

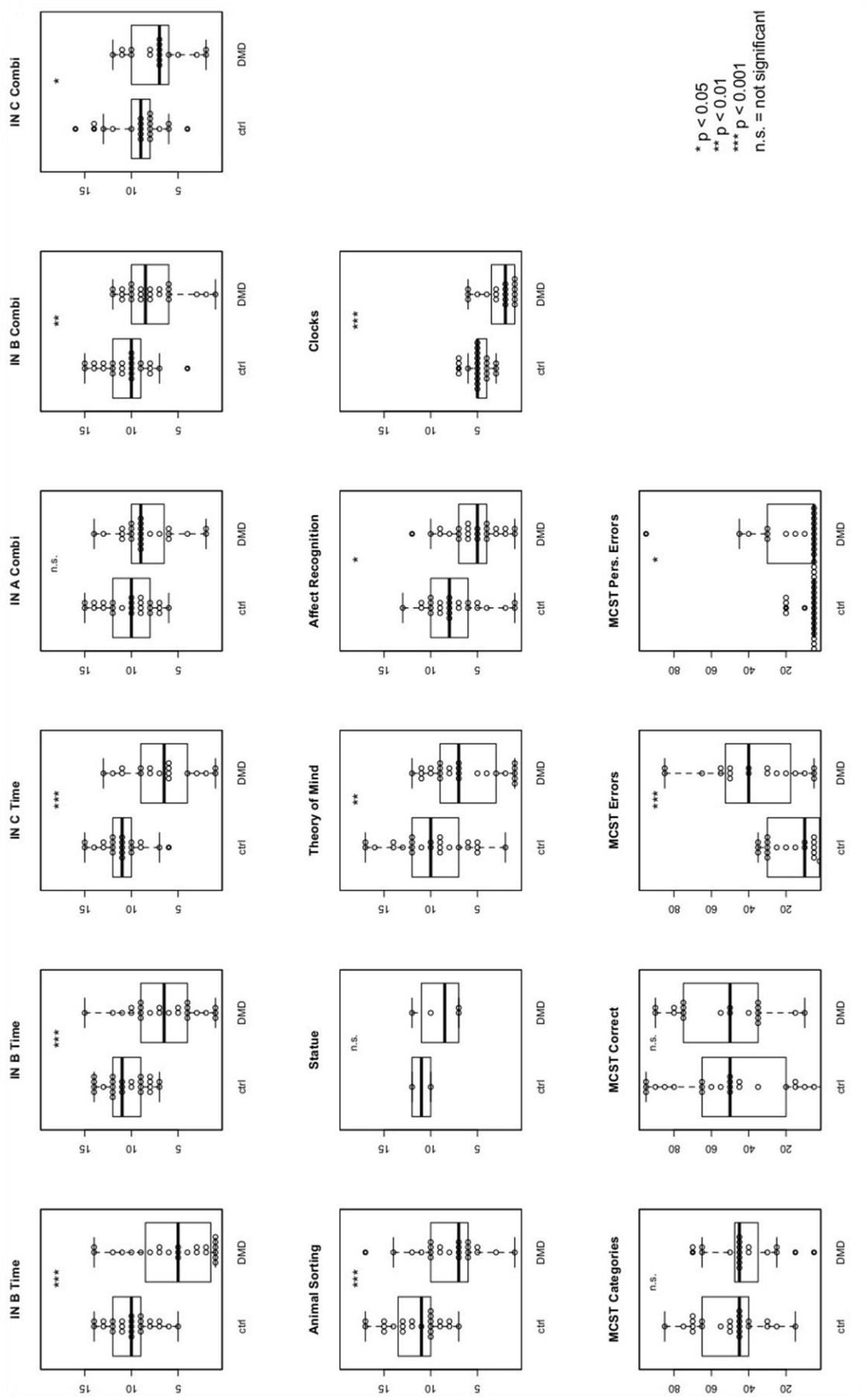
Table 2: DMD patients and healthy controls on Empathy task

NEPSY II task	DMD					CONTROLS					
	n	M	SD	min	max	n	M	SD	min	max	p-value
Theory of Mind	25	6,6	3,8	1	12	25	10,0	4,0	2	17	0,005 **
Affect Recognition	25	5,4	2,8	1	12	25	7,4	3,1	1	13	0,01 *

Significance levels: * p < 0.05; ** p < 0.01; *** p < 0.001

Control sample exhibited a good performance in the ToM test (mean=10, SD=3.98) while the performance on the Affect Recognition test, even if better than the DMD group, was below normal range (mean=7.44, SD=3.11).
Results can be seen also in Boxplot 1.

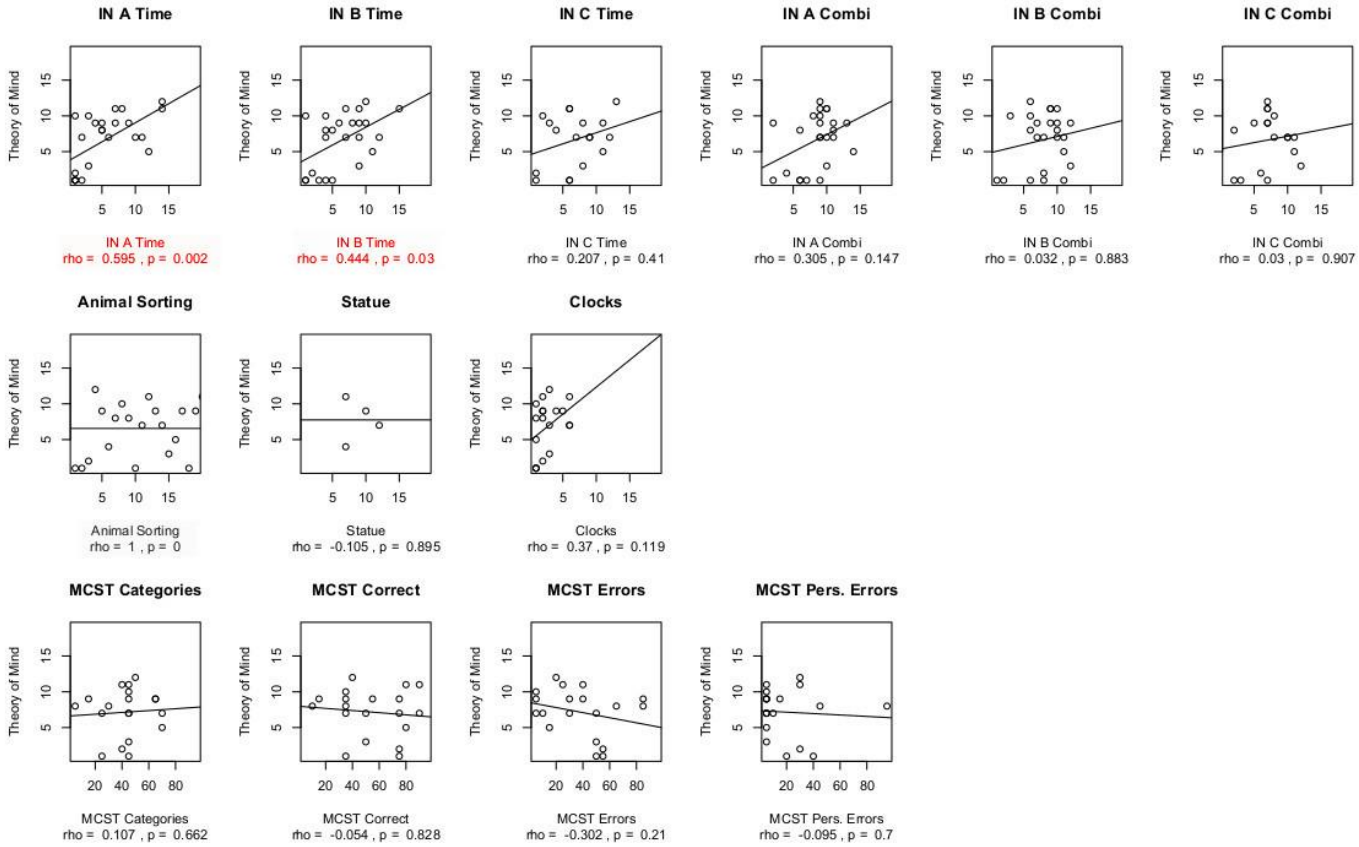
Boxplot 1: DMD vs healthy controls, Neuropsychological Evaluation



Correlation between Executive Functioning and Empathy tasks

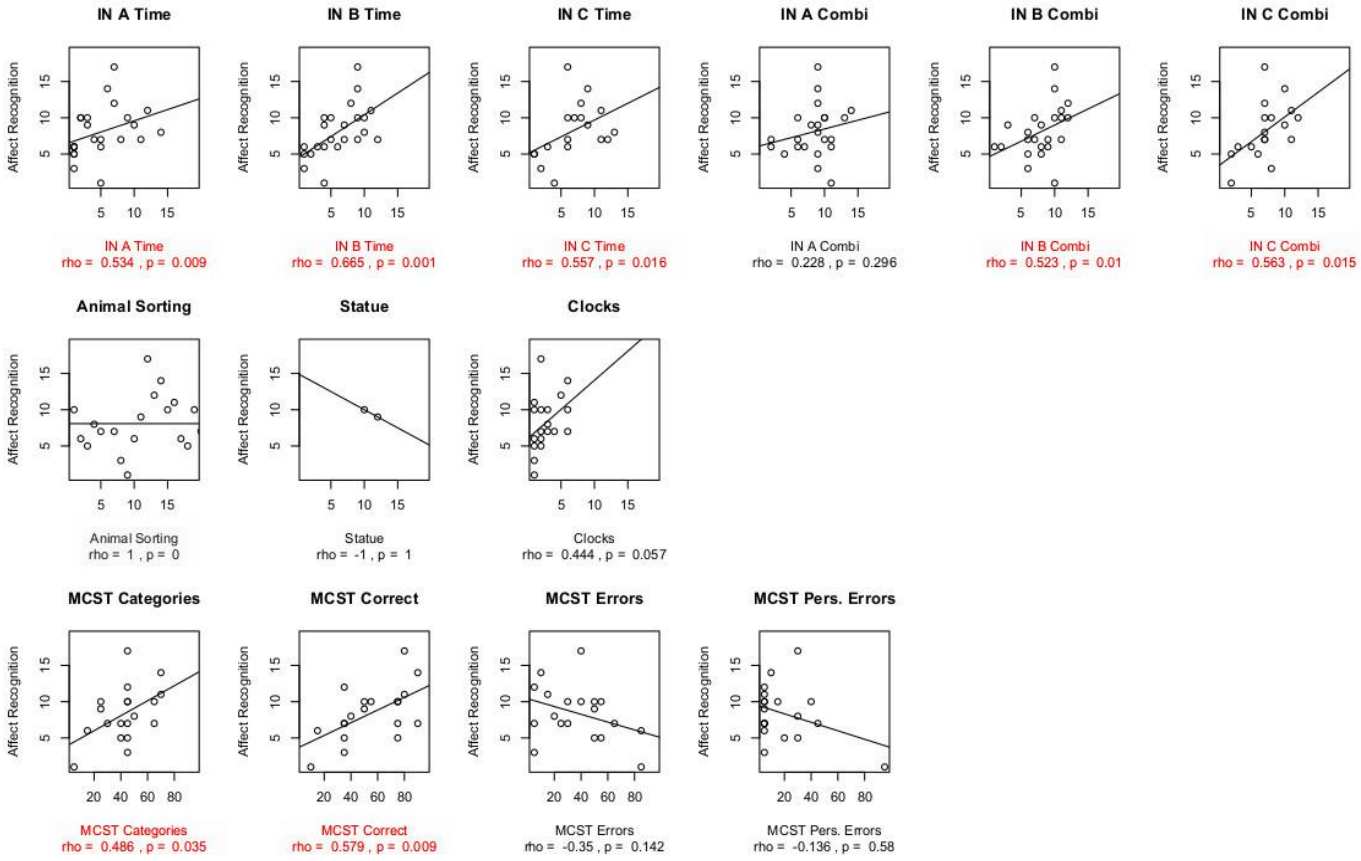
Considering the relation between the tests assessing EFs and the task regarding Cognitive Empathy, it emerged e significant correlation between the ToM task and two subscales of the Inhibition test (Inhibition_A_time: rho= 0.595, p= 0.002; Inhibition_B_time: rho= 0.444, p= 0.03).
Results can be seen in Boxplot 2.

Boxplot 2: DMD, Executive Functions and Theory of Mind



Positive correlations were found also between EFs tasks and the Affective Empathy test. In particular, Affect Recognition task correlated with all the three time scores of the Inhibition test (A: rho= 0.534, p= 0.009; B: rho= 0.665, p= 0.001; C: rho= 0.557, p= 0.016), and the combined scores of the subscale B and C of the Inhibition test (B: rho= 0.523, p= 0.01; C: rho= 0.563, p= 0.015). Moreover, it emerged a correlation with the two scores of the MCST (categories: rho= 0.486, p= 0.035; correct answers: rho= 0.579; p= 0.009) as showed by Boxplot 3.

Boxplot 3: DMD, Executive Functions and Affective Empathy



DMD and Control group on Emotion errors

Boxplot 4 illustrate the type of errors that experimental group and the control sample made on the Affect Recognition task while Table 3 reports the descriptive statistics of DMD patients and healthy controls relatively to emotions errors. Table 4 reports the ANCOVAs' results.

Participants' age was a statistically significant covariate for Happiness (p= 0.00554) and Disgust (p= 0.0366), while the presence of the disease was found statistically significant for Neutral (p= 0.00985) and Anger (p= 0.00226). In particular, DMD patients made significantly more errors relative to healthy controls as regard the emotions Neutral and Anger.

Boxplot 4: DMD vs healthy controls, emotions errors

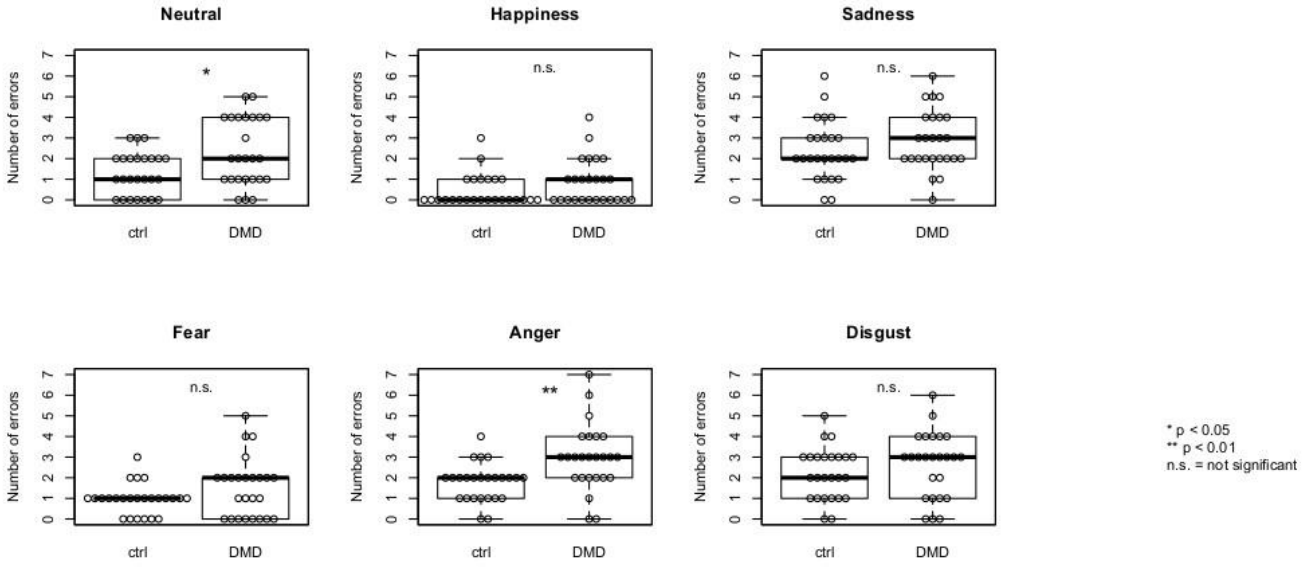


Table 3: DMD patients and healthy controls on emotions errors

EMOTIONS	DMD					CONTROLS				
	n	M	SD	min	max	n	M	DS	min	max
Neutral	25	2,3	1,6	0	5	25	1,3	1,0	0	3
Happiness	25	0,9	1,1	0	4	25	0,4	0,8	0	3
Sadness	25	2,9	1,5	0	6	25	2,4	1,4	0	6
Fear	25	1,5	1,4	0	5	25	1,0	0,7	0	3
Anger	25	3,0	1,6	0	7	25	1,8	0,9	0	4
Disgust	25	2,6	1,6	0	6	25	2,2	1,3	0	5

Table 4: ANCOVA's results

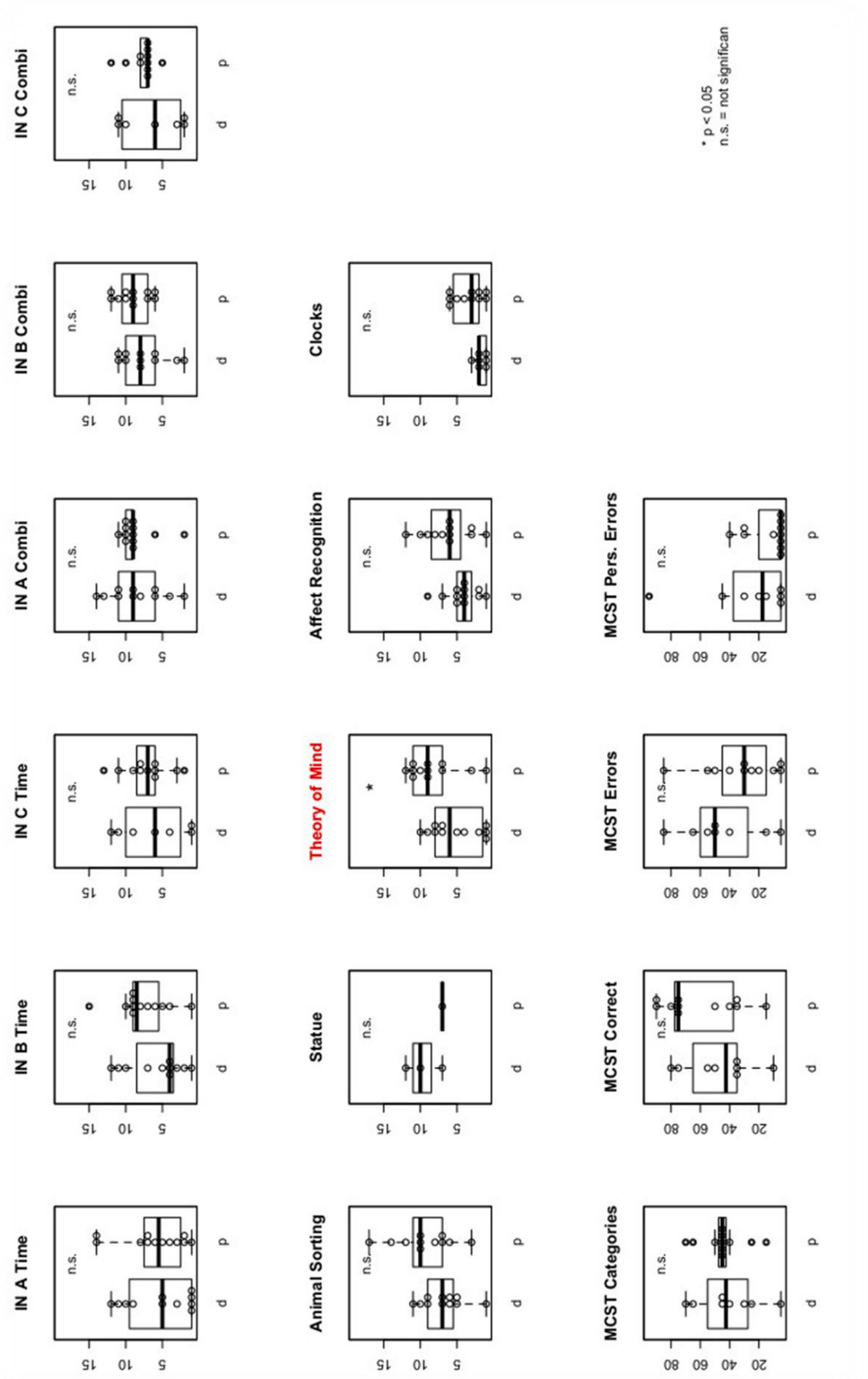
Response	Predictor	Sum of Square	df	Mean Square	F	Significance
NEUTRAL	Disease	13,52	1	13,52	7,24	**0,00985****
	Age	0,68	1	0,68	0,37	0,54826
	residuals	87,80	47	1,87		
HAPPINESS	Disease	2,42	1	2,42	3,14	0,08308
	Age	6,53	1	6,53	8,46	**0,00554****
	residuals	36,27	47	0,77		
SADNESS	Disease	2,88	1	2,88	1,36	0,249
	Age	1,37	1	1,37	0,65	0,424
	residuals	99,27	47	2,11		
FEAR	Disease	13,52	1	13,52	7,24	0,0888
	Age	0,68	1	0,68	0,37	0,7103
	residuals	87,80	47	1,87		
ANGER	Disease	18,00	1	18,00	10,44	**0.00226 ****
	Age	0,46	1	0,46	0,27	0,60799
	residuals	81,06	47	1,73		
DISGUST	Disease	2,42	1	2,42	1,28	0,264
	Age	8,77	1	8,77	4,63	**0.0366 ***
	residuals	88,99	47	1,89		

Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Dystrophin Mutation

Comparing the performance of DMD patients carrying proximal mutations relatively to intron 44 and subjects with distal mutations involving the distal portion of intron 44, it emerged an important and significant difference (p= 0.03) in the ToM test, in which DMD patients carrying proximal mutations showed a better performance relatively to patients with distal mutations. Moreover, the performance of DMD patients affected by distal mutations was more than 1 SD below normal range while the performance of patients with proximal mutations was comparable to normative data, as it can be seen on Boxplot 5.

Boxplot 5: DMD, Neuropsychological Evaluation and Dystrophin Mutation



7.2. BECKER MUSCULAR DYSTROPHY

BMD and Control group on Executive Function evaluation

Comparing the performance of BMD patients and the control group on the test assessing EFs, it emerged a worse performance for BMD patients relatively to healthy subjects on the FAS test (p= 0.01).

On the other hand, BMD patients showed a better performance relatively to the control group on the DS_f test (p= 0.04).

Result can be seen in Table 5 and Boxplot 6.

Table 5: BMD patients and healthy controls on Executive Functions assessment

TEST	BMD					CONTROLS					
	n	M	SD	min	max	n	M	SD	min	max	p-value
Digit Span forwards (DS_f)	21	6,1	1,0	6	8	21	5,6	0,7	4	7	0,04 *
Digit Span backward (DS_b)	21	4,3	1,0	3	6	21	4,1	0,9	3	6	0,46
Phonemic Fluency (FAS)	21	38,1	14,0	22	74	21	46,2	11,6	24	70	0,01 *
Trial Making Test B-A (TMT)	21	42,3	29,7	9	130	21	34,4	16,9	7	74	0,58
MCST Perseverative Errors	21	1,3	1,7	0	5	21	0,3	0,7	0	2	0,48
MCST Category	21	5,5	1,0	3	6	21	6,0	0,2	5	6	0,46

Significance levels: * p < 0.05; ** p < 0.01; *** p < 0.001

BMD and Control group on Empathy tasks

Focusing the attention on the comparison between the experimental and the control group relatively to the performance on Empathy tasks, it could be notice no relevant differences between the two groups except for a significantly higher score of BMD patients on the Empathic Concern scale of IRI questionnaire (p= 0.03) comparing to healthy participants.

Results are illustrated in Table 6 and Boxplot 7.

Boxplot 6: BMD vs healthy controls on Executive Functions assessment

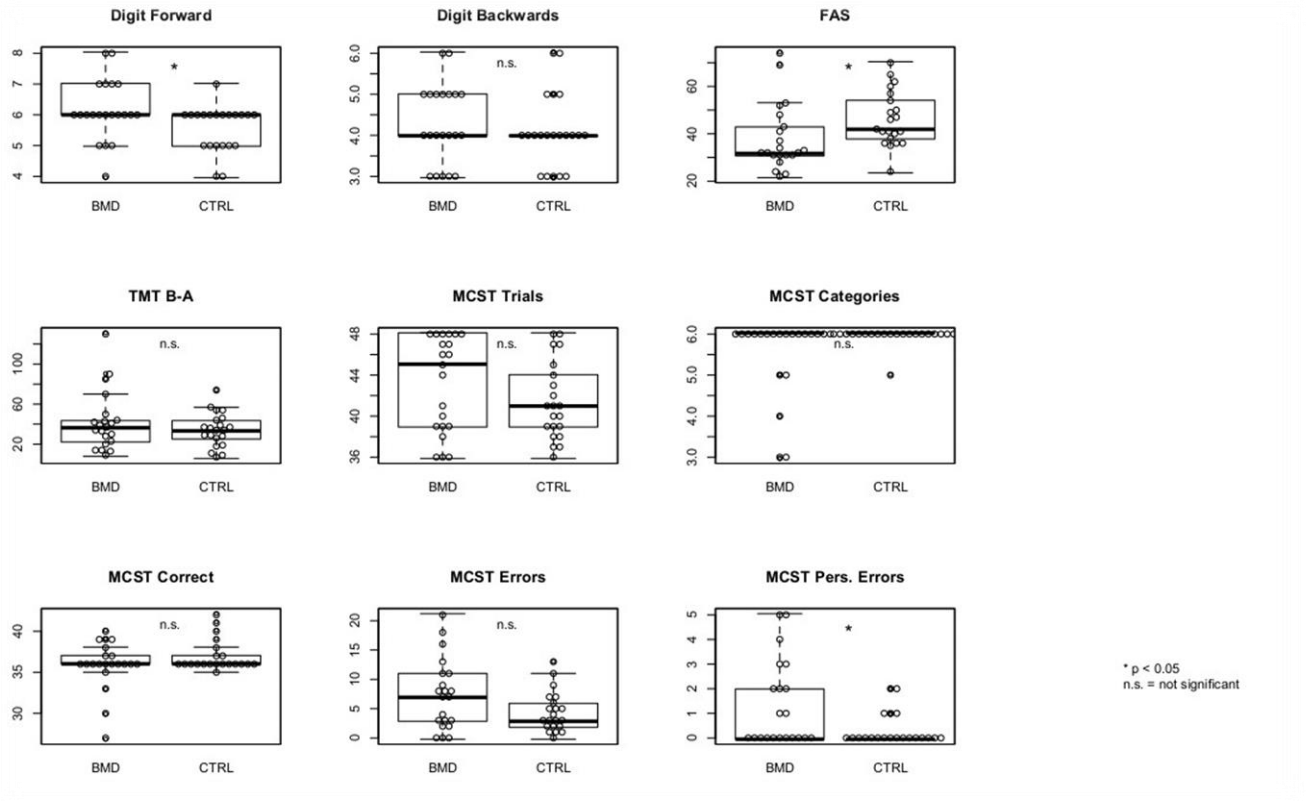
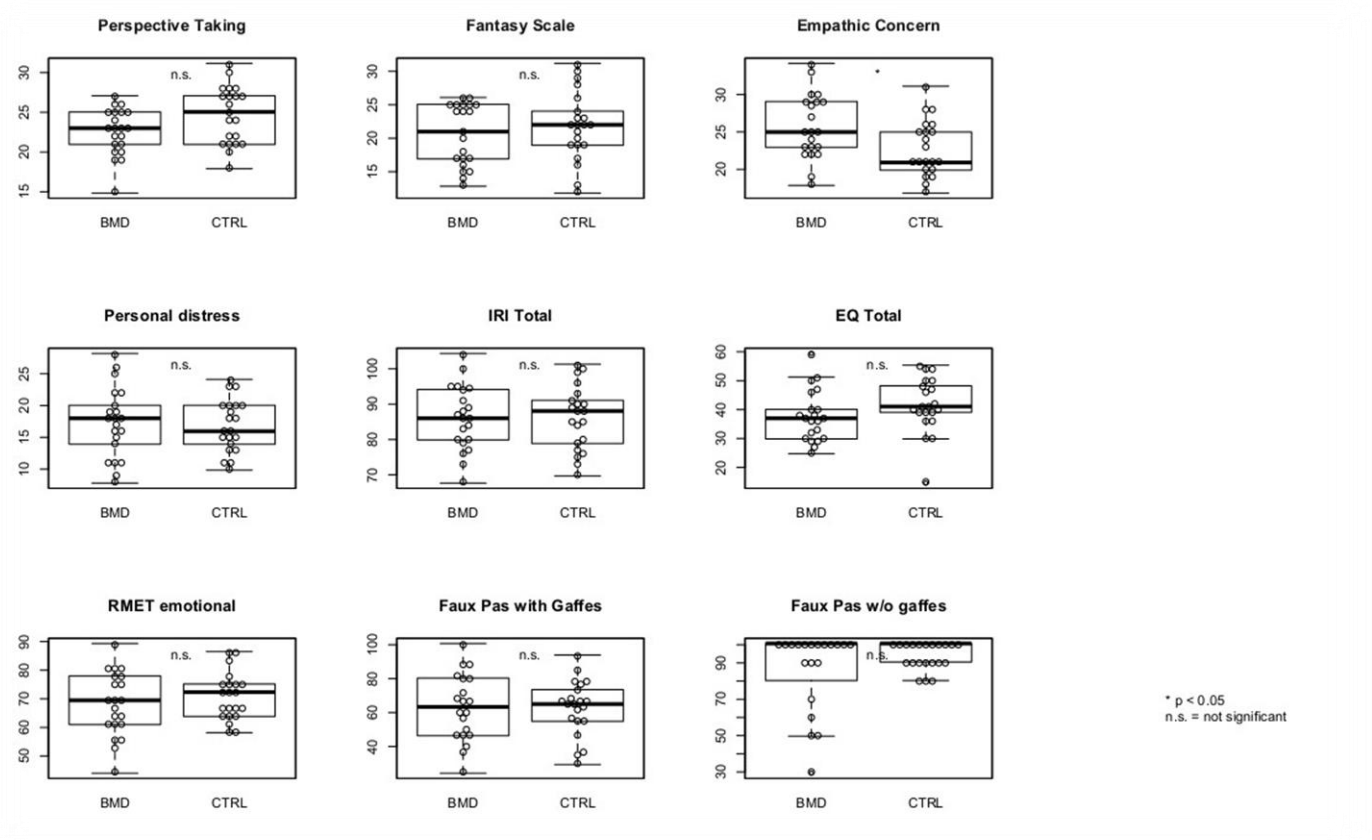


Table 6: BMD patients and healthy controls on Empathy task

TEST AND QUESTTIONNAIRES	BMD					CONTROL					
	n	M	SD	min	max	n	M	SD	min	max	p-value
Reading the Mind in the Eyes (RMET_emotional)	21	68,1	11,1	44	88	21	70,8	8,3	53	86	0,52
Interpersonal Reactivity Index (IRI_tot)	21	86,2	9,1	68	104	21	86,1	9,0	70	101	1
Empathic Concern (EC_IRI)	21	25,7	4,3	18	34	21	22,8	3,7	17	31	0,03 *
Fantasy Scale (FS_IRI)	21	20,6	4,6	13	26	21	21,8	5,1	12	31	0,61
Personal Distress (PD_IRI)	21	17,3	5,5	8	28	21	16,9	4,1	10	24	0,86
Perspective Taking (PT_IRI)	21	22,6	2,9	15	27	21	24,7	3,6	18	31	0,06
Empathic Quotient (EQ_tot)	21	37,6	8,8	25	59	21	41,5	9,4	15	55	0,06
Faux Pas-with gaffes (FPt)	21	63,0	19,7	25	100	21	63,0	16,2	30	93	0,97
Faux Pas without gaffes (FPt)	21	86,5	21,8	30	100	21	93,8	7,4	80	100	0,97

Significance levels: * p < 0.05; ** p < 0.01; *** p < 0.001

Boxplot 7: BMD vs healthy controls on Empathy tasks



Correlation between Executive Functions and Empathy tasks

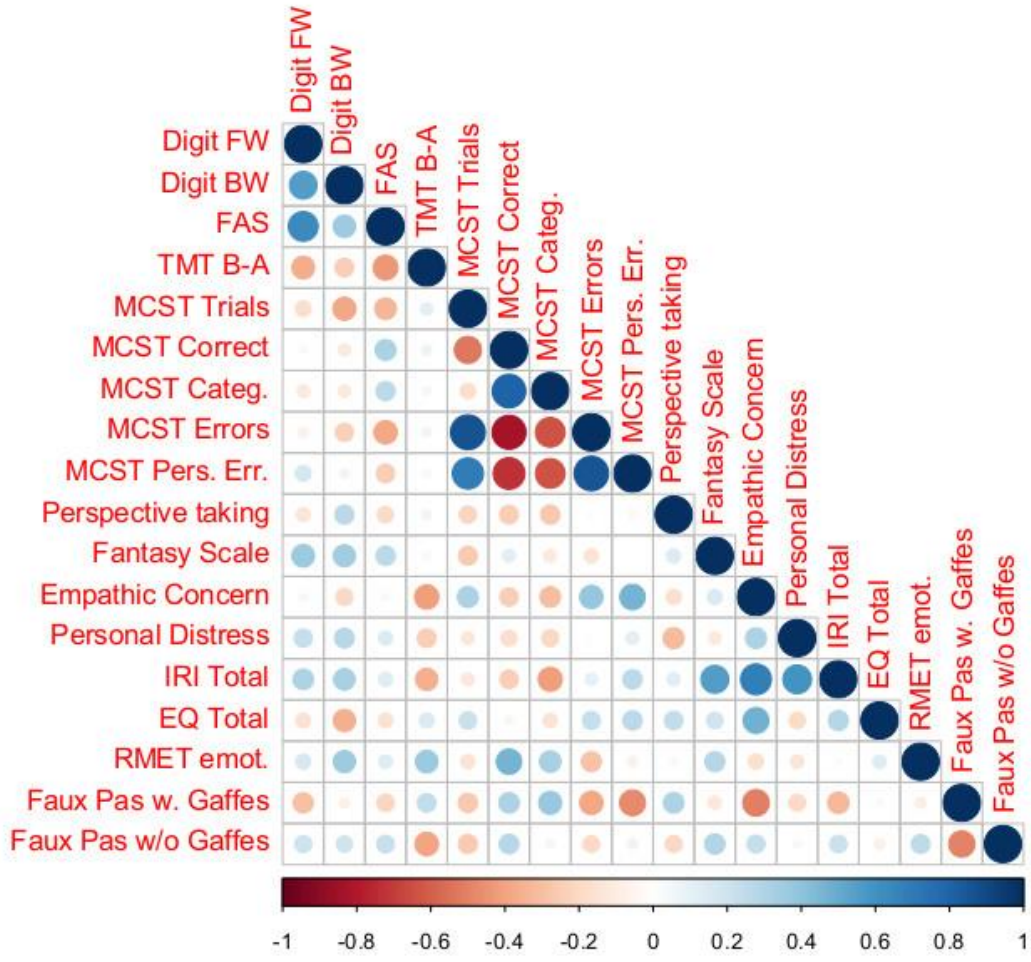
Subsequently, it has been investigated the presence of a relation between the tasks assessing EF and the tests and questionnaires related to Empathy abilities.

As regards BMD patients, it emerged a significant negative correlation between the score related to the FPt, stories with gaffes, and the score representing the perseverative errors of MCST (rho= -0,47; p= 0,031).

No significant correlations were found between Affective Empathy tasks and EFs tests.

Correlations between EFs and Empathy tasks can be seen in Graphic 1.

Graphic 1: BMD, correlation between Executive Functions and Empathy



Dystrophin Mutation

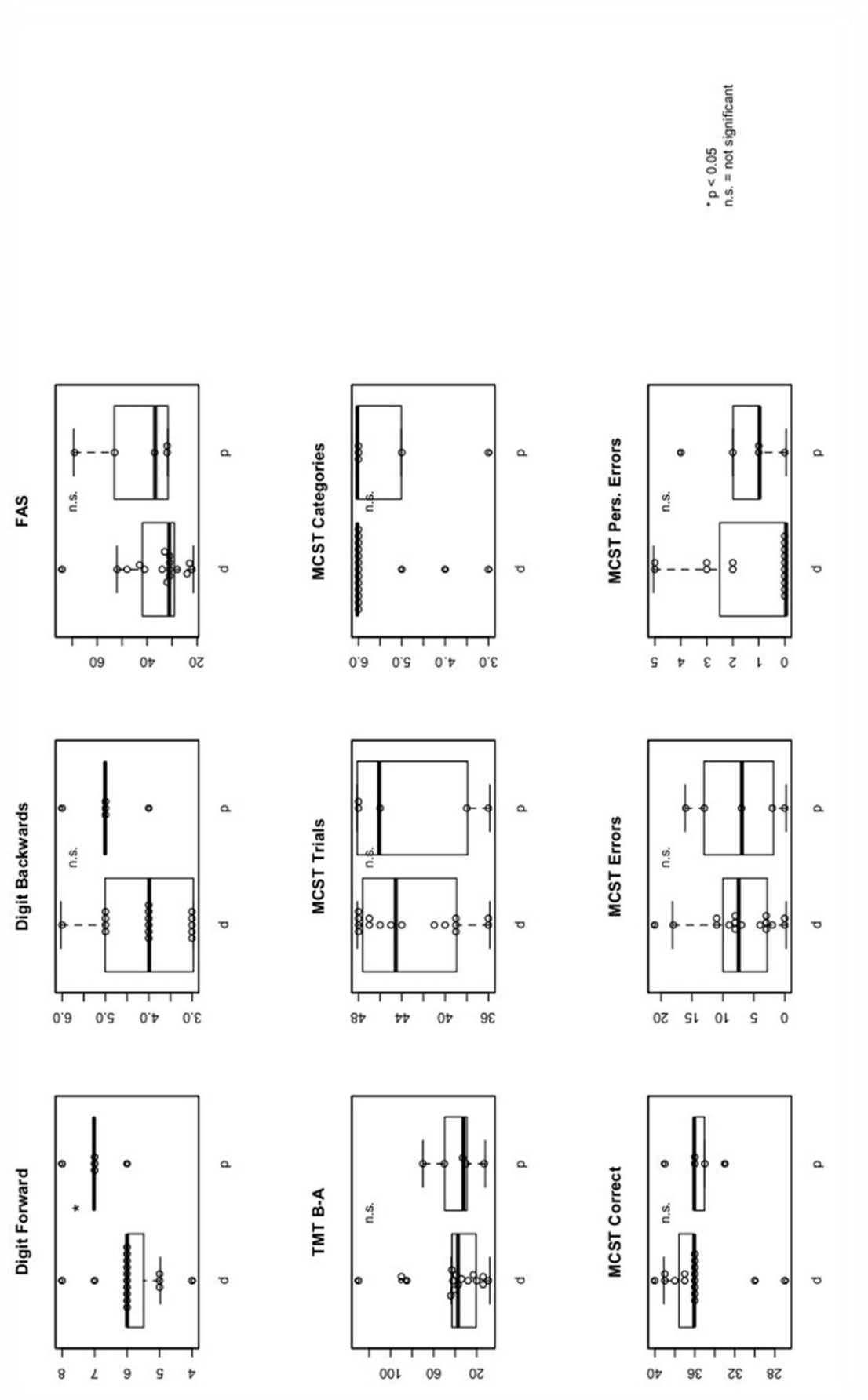
Lastly, we investigated the relation between the kind of mutation on dystrophin gene and the cognitive performance of BMD patients.

As for DMD patients, we distinguished between BMD subjects with distal mutations and patients affected by proximal mutations.

From data analysis, it emerged that BMD patients with proximal mutations had a significantly better performance relatively to BMD patients carrying distal mutations in the DS_f test (p= 0,014).

Results are illustrated in Boxplot 8.

Boxplot 8: BMD, Executive Functions and Dystrophin Mutation



7.3. FACIOSCAPULOHUMERAL DYSTROPHY

FSHD and Control group on Executive Functioning

Comparing the experimental group and the control sample as regards the performance on cognitive tasks, no differences emerged between the two groups, as shown in Table 7.

Table 7: FSHD patients and healthy controls on Executive Functions assessment

TEST	FSHD					CONTROLS					
	n	M	SD	min	max	n	M	SD	min	max	p-value
Digit Span forwards (DS_f)	21	6,1	0,7	5	7	21	5,9	1,0	4	8	0,23
Digit Span backward (DS_b)	21	4,2	0,6	3	5	21	4,2	0,8	3	6	0,74
Phonemic Fluency (FAS)	21	43,0	12,5	21	77	21	47,0	12,3	24	78	0,22
Trial Making Test B-A (TMT)	21	46,5	32,0	10	134	21	48,0	28,3	11	131	0,69
MCST Perseverative Errors	21	0,3	0,7	0	2	21	0,8	1,7	0	7	0,47
MCST Category	21	5,9	0,4	5	6	21	5,7	1,1	1	6	0,70

Significance levels: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

FSHD and Control group on Empathy tasks

As regards the performance on tasks and questionnaires assessing Empathy abilities, FSHD patients and the control sample were indistinguishable as regards ToM tasks.

On the contrary, FSHD showed significantly higher scores in the Empathic Concern scale of IRI questionnaire ($p= 0.02$) and in the total score referred to the EQ ($p= 0.04$), measures of Affective Empathy.

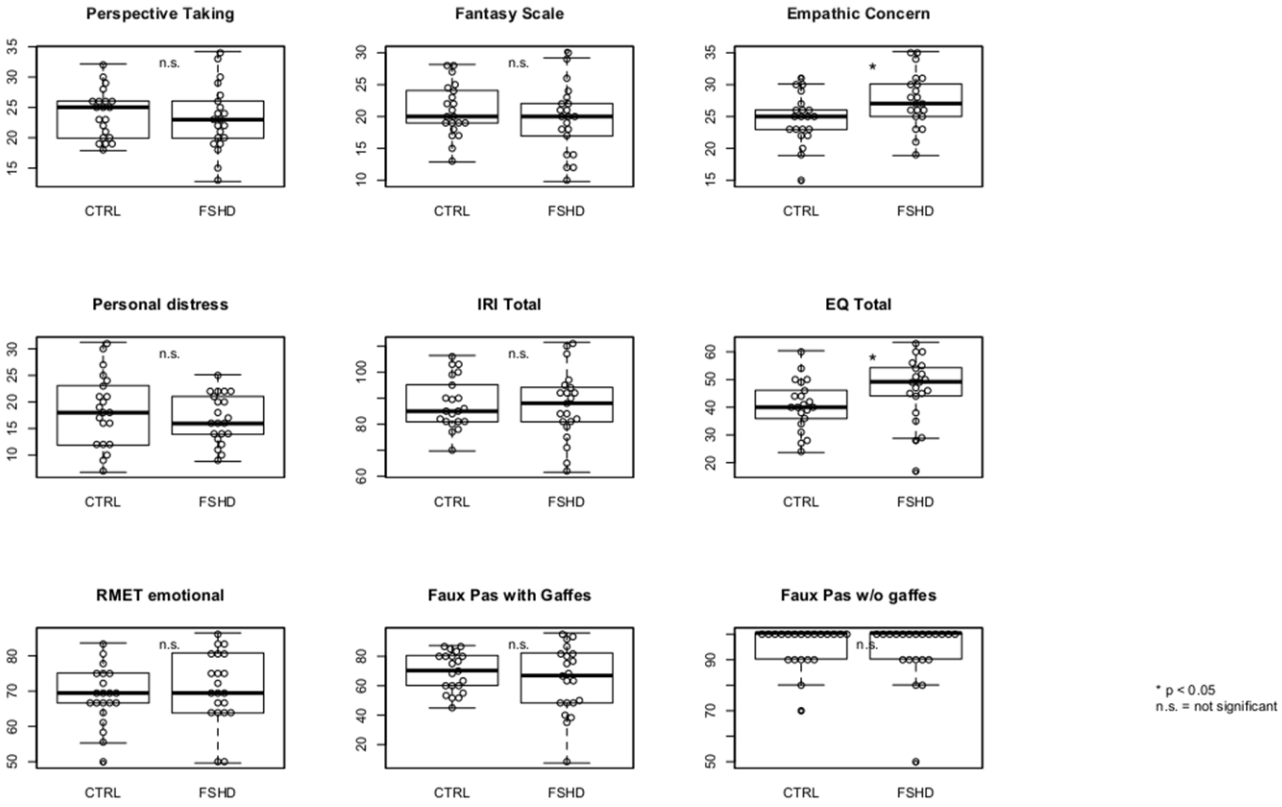
Results are illustrated in Table 8 and Boxplot 9.

Table 8: FSHD patients and healthy controls on Empathy task

TEST AND QUESTIONNAIRES	FSHD					CONTROLS					
	n	M	SD	min	max	n	M	SD	min	max	p-value
Reading the Mind in the Eyes (RMET_emotional)	21	70,9	10,0	50	86	21	68,5	8,1	50	83	0,39
Interpersonal Reactivity Index (IRI_tot)	21	87,2	13,2	62	111	21	87,9	9,8	70	106	1
Perspective Tacking (PT_IRI)	21	23,2	5,4	13	34	21	23,9	4,0	18	32	0,59
Fantasy Scale (FS_IRI)	21	19,6	5,3	10	30	21	21,0	4,1	13	28	0,45
Empathic Concern (EC_IRI)	21	27,6	4,3	19	35	21	24,5	3,9	15	31	0,02 *
Personal Distress (PD_IRI)	21	16,9	4,6	9	25	21	18,5	6,7	7	31	0,50
Empathic Quotient (EQ_tot)	21	46,3	11,5	17	63	21	40,8	9,1	24	60	0,04 *
Faux Pas-with gaffes (FPt)	21	63,8	22,8	8	95	21	69,1	13,3	45	87	0,56
Faux Pas without gaffes (FPt)	21	93,3	12,0	50	100	21	95,2	8,1	70	100	0,71

Significance levels: * p < 0.05; ** p < 0.01; *** p < 0.001

Boxplot 9: FSHD vs healthy controls on Empathy task



Correlation between Executive Functions and Empathy tasks

Investigating the relation between EFs and Empathic abilities in FSHD patients, it emerged that the TMT B-A score was related both to the Empathic Concern scale of IRI questionnaire (rho= 0.53; p= 0.013) and to the total score of IRI questionnaire (rho= 0.45; p= 0.039), as it can be seen in Graphic 2.

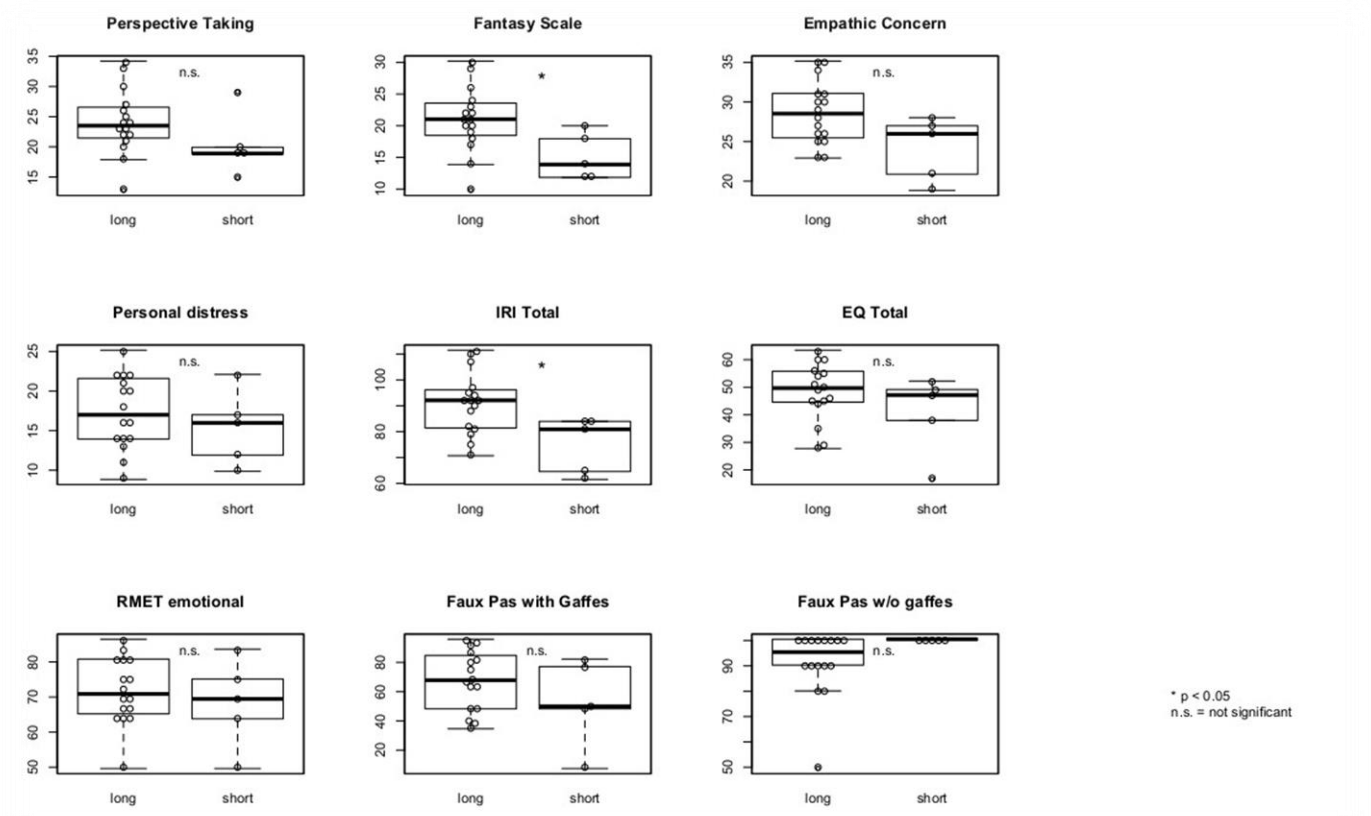
EcoRI Fragment size

Finally, the investigation of the relation between the EcoRI fragment size of FSHD patients and the neuropsychological assessment revealed a correlation between the fragment size and the Fantasy scale score of IRI questionnaire (p= 0.03) and the total score of IRI questionnaire (p= 0.03).

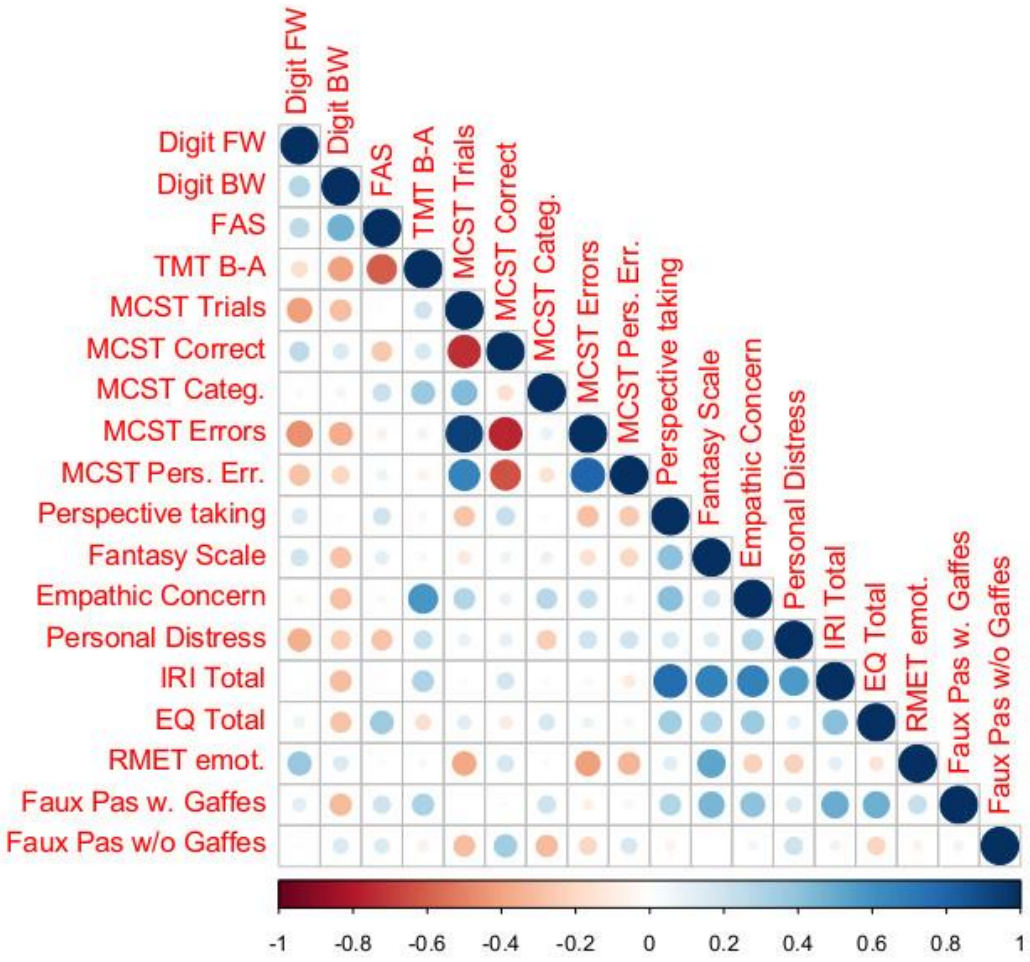
More precisely, patients carrying a shortest EcoRI fragment size (<24Kb) showed a worse performance relatively to patients with a long fragment size (≥ 24 Kb).

Results are illustrated in Boxplot 10.

Boxplot 10: FSHD, Empathy and EcoRI Fragment size



Graphic 2: FSHD; correlation between Executive Functions and Empathy



7.4. X-LINKED SPINAL and BULBAR MUSCULAR ATROPHY

SBMA and Control group on Executive Functioning

Table 9 reports the descriptive statistics of SBMA patients and healthy controls while Table 10 reports the ANCOVAs' results.

Education level was a statistically significant covariate for all the neuropsychological measures, while participants' age was found statistically significant for the TMT test (p= 0.032) and the DS_f test (p= 0.016).

There was a statistically significant difference between groups for the Babcock Story Recall Test score, with patients performing better than control participants (p= 0.006).

Results can be seen also in Boxplot 11.

Table 9: SBMA patients and healthy controls on Executive Functions assessment

TEST	SBMA					CONTROLS				
	n	M	SD	min	max	n	M	SD	min	max
Digit Span forwards (DS_f)	70	5.83	1.23	3	9	78	5.93	1.21	4	9
Digit Span backward (DS_b)	70	4.41	1.14	2	8	78	4.10	1.00	2	6
Phonemic Fluency (FAS)	70	38.73	10.34	15	71	78	35.79	11.49	14	63
Trial Making Test B-A (TMT)	70	57,3	0,5	13	223	78	50,1	44,2	-34	210
Babcock story recall total (prose)	70	13.54	2.58	6,1	18	78	12.35	2.57	4	16

Correlation between Executive Functions and Neurological Measures

It has been investigated in there was a relation between the cognitive performance of SBMA patients and the neurological measures, in particular 6MWT and ALSFRS.

Analysis revealed no correlation between these two aspects.

Table 10: SBMA, ANCOVA's results

Response	Predictor	Sum of Square	Df	F	Significance	Partial eta^2	Cohen's d †
Digit Span_forward (DS_f)	Age	1.23	1	5.97	**0.016** *	0.04	0.07
	Education	3.55	1	17.19	**< 0.001** ***	0.12	
	Group	0.03	1	0.13	0.715	<0.01	
	Residuals	27.23	132				
Digit Span_backward (DS_b)	Age	0.60	1	2.50	0.117	0.02	0.34
	Education	2.39	1	9.94	**0.002** **	0.08	
	Group	0.84	1	3.50	0.064	0.03	
	Residuals	26.96	112				
Phonemic Fluency (FAS)	Age	21.39	1	0.19	0.660	0.00	0.28
	Education	1321.87	1	12.00	**< 0.001** ***	0.08	
	Group	293.70	1	2.67	0.105	0.02	
	Residuals	14544.48	132				
Babcock story total (Prose)	Age	15.40	1	2.42	0.123	0.02	0.50
	Education	13.81	1	2.17	0.143	0.02	
	Group	50.42	1	7.91	**0.006** **	0.06	
	Residuals	802.78	126				
Trial Making Test (TMT)	Age	1.85	1	4.70	**0.032** *	0.04	0.24
	Education	3.70	1	9.38	**0.003** **	0.07	
	Group	0.72	1	1.83	0.179	0.01	
	Residuals	47.70	121				

†: Computed on adjusted scores; Significance levels: * p < 0.05; ** p < 0.01; *** p < 0.001

PolyQ/ Testosterone levels and Executive Functions

It has been investigated in there was any relation between the cognitive performance of SBMA patients and the PolyQ expansion or Testosterone levels.

The within-group regression analyses, reported in table 11, did not show evidences for any of the hypothesized effects. All of the models showed no statistical significance and a very low R^2.

Boxplot 11: SBMA vs healthy controls on Executive Functions assessment

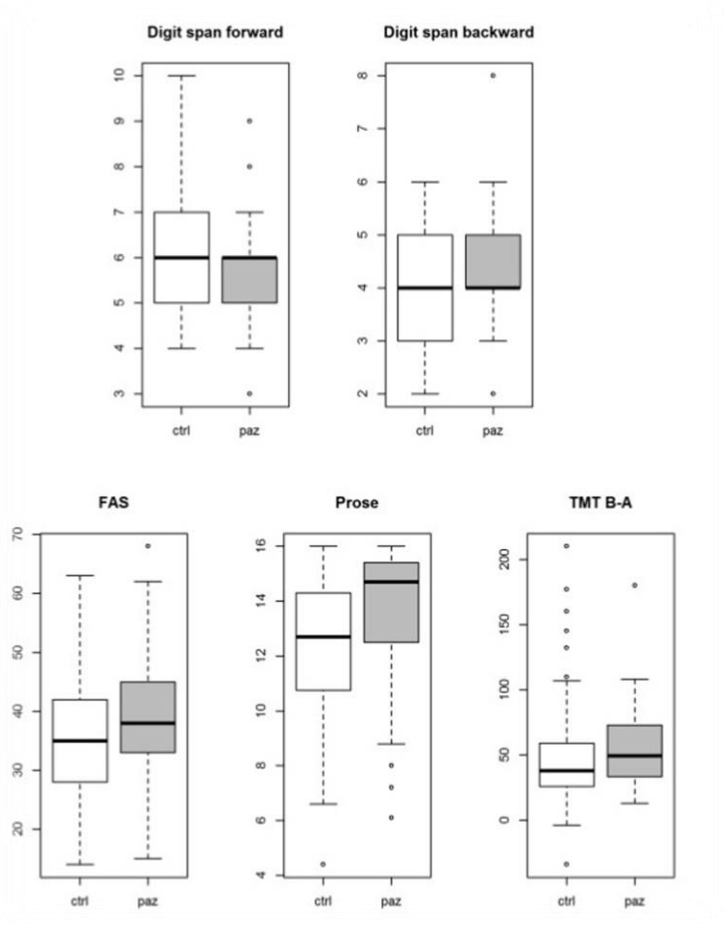


Table11: SBMA, regression analyses

Response		PoliQ	Testosterone	Interaction	F	num df	den df	p-value	Adj. R^2
Digit Span forward (DS_f)	Estimate	0.016	0.025	0.000					
	t	0.239	0.182	-0.152	0.128	3	59	0.943	-0.044
	p-value	0.812	0.856	0.880					
Digit Span backward (DS_b)	Estimate	-0.026	-0.108	0.002					
	t	-0.33	-0.661	0.646	0.419	3	59	0.740	-0.029
	p-value	0.743	0.511	0.521					
Phonemic Fluency (FAS)	Estimate	0.395	-0.504	0.012					
	t	0.272	-0.166	0.181	0.662	3	58	0.579	-0.017
	p-value	0.787	0.869	0.857					
Babcock Story total (Prose)	Estimate	-0.165	-0.675	0.015					
	t	-0.434	-0.851	0.847	0.670	3	58	0.574	-0.016
	p-value	0.666	0.398	0.401					
Trial Making Test (TMT)	Estimate	-0.005	-0.016	0.000					
	t	-0.071	-0.111	0.072	0.146	3	59	0.932	-0.043
	p-value	0.944	0.912	0.943					

8. DISCUSSION

8.1. DUCHENNE MUSCULAR DYSTROPHY

Considering the patients affected by DMD and the evidences emerged from literature as regards cognitive impairment and behavioral problems often detectable in DMD children, we expected a worse performance of DMD patients relatively to healthy controls on EFs tests. Moreover, we foresaw a worse performance of DMD children also in Empathy tasks, in particular in those assessing ToM.

Actually, from data analysis, pediatric patients affected by DMD showed a worse performance in most of the tests proposed for EFs assessment relatively to healthy controls. Moreover, for DMD patients, the mean in four of the scores computed suggested a performance under the cut-off of normality. These results are in line with previous researches made on DMD patients that highlighted deficits on attention and EF in this population (Anderson et al., 1998; Cotton et al., 1998; De Moura et al., 2010; Donders & Taneja, 2009; Mento et al., 2011; Wicksell et al., 2004; Wingeier et al., 2011).

Nowadays, few studies have investigated the cognitive profile of DMD patients in pediatric age using the battery NEPSY-II. Among them, the study of Cyrulnik et al., (2008), in which the Authors used the first version of NEPSY with the aim to examine the cognitive skills of DMD children, revealed impairment in multiple measures of cognition. However, DMD sample was composed only by children between 3 and 6 years old. Marini et coll. (2007), instead, proposed some subtests of the first version of NEPSY with the aim to assess narrative abilities of DMD patients; EFs were not evaluated.

Our sample of DMD patients revealed particular difficulties in performing the Inhibition test. Actually, they showed a worse performance, relatively to control participants, in five of the six scores that compose the subtest. Moreover, all the tree scores concerning the time needed to complete the task revealed a performance under the cut-off of normality.
The Inhibition test requires to name the shape of squares and circles or the up or down direction of the arrows. The stimuli presented are forty for each of the six conditions.

A low score concerning “time” means that the participant has employed a long time to complete the task if compared to normative data.
As regards the conditions “inhibition” and “switching”, it can be supposed that DMD children had more difficulties, compared to healthy children, in inhibiting the automatic responses suggested by the task and in using new counterintuitive responses so that these children needed more time to complete appropriately the task. However, this explanation can’t justify the score relative to the “denomination” subtest, in which the participant had only to say the name of the figure he saw. As reported in the NEPSY II manual (Korkman, 2007), the performance in the Inhibition test can be influenced also by perceptive abilities, Working Memory and articulation skills. Poor expressive verbal abilities and deficits in verbal working memory have been revealed in DMD patients (Karagan et al., 1980; Hinton et al., 2000). Probably, difficulties in one of these aspects have influenced the performance of DMD patients in the Inhibition test.
An interesting finding regards the performance on the Clocks test. The task has been carried out by 19 DMD and 23 controls. Fourteen of the nineteen DMD children had a performance under the cut-off of normality (set to a standardize score less than the 10 percentile, as suggested by the Authors of NEPSY II) while only one of the twenty-three controls failed in this task. Moreover, two of the DMD patients that didn’t complete the test, and so that were not considered in the mean score, were respectively 10 and 11 years old. Also during the administration of the cognitive assessment, it was evident an important lack of knowledge about analogical clocks, not only related to the reading of the hours but also regarding the placement of the numbers in the watch dial. Considering the fact that literature doesn’t report overt deficits on visuospatial abilities in DMD children (Karagan et al., 1980; Cyrulnik et al.,2008; Hinton et al.,2000; Billard et al., 1992), the performance could be explained by simply ignorance about analogical clocks.

Furthermore, DMD patients showed a worse performance, in comparison to healthy controls, also relatively to the ToM test, assessing Cognitive Empathy, and the Affect Recognition test, concerning Affective Empathy. Of particular interest is the fact that the mean scores of DMD children on both the tasks is more than one standard deviation under the cut-off of normality. This mean that not only the performance of DMD is scarce but also that is insufficient considering normative data.

The impaired performance of DMD patients as regards the ToM task is in line with the preliminary hypothesis, considering the deficit existing in the sample relatively to EF and the relation between EFs and Cognitive Empathy (Russell, 1997; Carlson et al., 2002).
Considering the Affect Recognition task, in which participants needed to match the two faces expressing the same emotion among three or more alternatives, EFs should not be primarily involved (Gallese, 2003). Probably, the difficulties reported in literature concerning social inhibition and the higher prevalence in DMD subjects, relatively to healthy population, of diseases related to Empathy, such as ASD and ADHD (Hinton et al., 2006; Hendriksen et al., 2008), resulted in problems regarding the ability to understand and share emotions of others. Thinking about Empathy as a linear construct (Davis, 1996), we can imagine that the achievement of Empathy abilities of DMD patients without overt ASD problems is still a few steps back relatively to healthy children and comparable to the performance of younger children.

The aim of this study was the investigation of the relation between EFs and Cognitive Empathy, considering the lack of evidences regarding this topic in literature and the impact that this information can have on clinical field.
In the present research, it emerged a correlation between the Inhibition test and the ToM task in DMD children.
Certainly, the Inhibition test is an accurate measure for skills that are classified in the realm of EF, such as the ability to inhibit automatic responses, replace old answers with new counterintuitive answers, constantly monitor the behavior, mental flexibility and Working Memory (Aron et al., 2004). So, the fact that the Inhibition test is related to the ToM task confirm the bound existing between EFs and Cognitive Empathy.

An extremely surprisingly result emerged correlating the tests assessing EFs and the Affect Recognition task. The test assessing Affective Empathy correlated with the measures of the Inhibition test and with the scores related to the MCST task. In this case the preliminary hypotheses have been disconfirmed.
Probably this result can be attributed to the dystrophin mutation; precisely, the lack of dystrophin in DMD children, that is present also in the CNS (Anderson et al., 2002) can affect different cerebral areas randomly. Actually, as described in chapter four, neuroimaging studies involving DMD patients shows disorders in CNS architecture, as dendritic abnormalities, neuronal loss, cortical atrophy and loss of Purkinje cells (Blake et al., 2000; Mehler et al., 2000), but these deficits are not related to

particular cortical or non-cortical areas. Moreover, it must be considered that the cerebral areas underpinning EFs and Cognitive Empathy are only partially overlapping (Zaki & Ochsner, 2012) and that there are brain regions implicated both in Cognitive and in Empathy tasks (Vollm et al., 2006).

Furthermore, it seemed interesting to investigate, in the two samples, the types of emotion errors made in the Affect Recognition test. From data analyses, it emerged that DMD patients made more errors compared to healthy children as regards the emotion Neutral and Anger. During the Affect Recognition task, participants could indicate one or two faces that expressed an emotion different from the one considered right for the task. All the wrong answers were collected so that it could be seen the type of errors made. As the performance on this test was significantly worse for DMD patients comparing to healthy controls, it was not surprising that the errors of DMD children for every emotion were more than the errors made by healthy controls. The interesting evidence was that, covariating the type of errors with age and group, the emotions Happiness and Disgust resulted to be related to the age of participants, and so younger children made more errors relatively to these two emotions in comparison to older children, while the emotions Neutral and Disgust were related to the membership group, with DMD wrongly identifying these two emotions, rather than giving the correct answer, more frequently in comparison to controls. The explanation that can be given to this evidence is that, as younger children indicate more frequently Happiness and Disgust because they are emotions easily identifiable comparing to subtler one, DMD children may indicate frequently faces expressing Neutral and Anger because they are the emotions that they see most often in their everyday life. Actually, for example, the stress experienced by DMD caregivers, caused by the disease progression and the behavioral characteristic of these children (Nereo et al., 2003; Kazak et al., 1987; Hinton et al., 2006; Reid and Renwick 2001), can unfortunately manifest also with the expression of negative emotions.

Finally, considering the location of the mutation in the dystrophin gene, we expected that DMD patients with distal mutations would perform worse relatively to DMD patients carrying proximal mutations on the neuropsychological evaluation. Actually, it emerged that DMD patients with mutations in the distal portion of the dystrophin gene had a significantly worse performance on the ToM test compared to DMD children carrying proximal mutations on the dystrophin gene.

More in depth, literature highlights that DMD patients carrying a mutations located in the distal portion of the dystrophin gene (involving the 140-kDa brain protein isoform, called Dp140) are

generally more severely affected and expressed different patterns of strengths and impairments, compared with DMD patients with mutations located in the proximal portion of the dystrophin gene (not involving Dp140). Considering cognitive abilities, DMD patients carrying distal mutations demonstrated specific impairments in visuospatial functions, visual memory and greater impairment in syntactic processing (D'Angelo et al., 2011).

The ToM test is a complex task as it requires the child to use multiple resources to be able to bring completed successfully. For example, the subject has to understand false beliefs in short stories and recognize the meaning of common saying and metaphors. This implicates that the child has to listen to what the examiner read, memorize the events that occurred, find if there's something wrong and formulate an acceptable and comprehensible response. Considering this, it can be that patients affected by distal mutations and with problems in visual memory and syntactic processing (D'Angelo et al., 2011) fail to complete the task successfully.

8.2. BECKER MUSCULAR DYSTROPHY

Considering the evidences provided by literature related to BMD, we expected from BMD patients a performance on the EFs tests and ToM tasks statistically comparable to the performance of the control group but slightly worse at a subclinical level. On the other hand, we foresaw that the performance on Affective Empathy tests would be statistically comparable to the performance of the control group.

As regards EF assessment, BMD patients showed a worse performance on the FAS test. This measure is really crucial in EF assessment: to complete the test participants have to cluster words in an unusual way, initiate numerous searches of subcategories, retrieve words within these subcategories and shift from one subcategory to another.

Moreover, FAS is sensitive to cognitive impairment from a variety of etiologies, for example deficits in FAS test are really sensitive to frontal brain damages (Troyer et al., 1998). Considering the cognitive assessment of ALS patients, a really invalidating neuromuscular disease, it emerged that the most striking and consistent deficit is found using tests of verbal fluency that results to be particularly sensitive to the impairment in these patients (Abrahams et al., 2000). For these reasons, a significant different performance between BMD patients and healthy controls in this test is a particularly relevant finding.

On the other hand, BMD patients had a better performance on DS_f task compared to controls. Actually, there are no evidences in literature regarding problems on short term memory capacity in these patient; this unexpected finding can be taken into account in future researches.

Furthermore, patients affected by BMD and healthy controls did not differed as regards the performance on the tests and questionnaires assessing Cognitive Empathy, result not expected considering the preliminary hypotheses. BMD ability to attribute mental states to others and appreciate the fact that can differ by their own resulted to be preserved, both considering self-report measures and as regards tasks specifically created for this evaluation. This result is in line with literature considering that has not been revealed dramatic behavioral and empathic problems in these patients (Grootenhuis et al., 2007)

Also as regards Affective Empathy the two samples showed a comparable performance but, surprisingly, BMD score on the Empathic Concern scale of IRI questionnaire resulted to be significantly higher relatively to healthy controls. The Empathic Concern scale assess "other-oriented" feelings of sympathy and concern for unfortunate others (Davis, 1980). It could be that their suffering, caused by the presence of an invalidating but not devastating disease and aggravated by the pain derived from muscular involvement (Zebraki & Drotar, 2008), together with preserved cognitive and empathic abilities, may have increased the sensitivity of BMD patients and lead them to be sincerely concerned about others' feelings.

As discussed for DMD patients, also in BMD participants we expected a correlation between the tests assessing ToM abilities and the tasks related to EFs; on the other hand, no correlation between EFs and the tasks assessing Affective Empathy was contemplated.
Investigating the relation between EFs and Cognitive Empathy, it emerged an important negative correlation between the FPt score relative to the stories with gaffes and the score related to the perseverative errors of the MCST. The score of the FPt stories with gaffes represents the number of correct answers given by the participant as regard the stories with faux pas while the perseverative errors score of the MCST indicates the number of perseverative errors made during the test. A negative correlation between these two scores means that the more correct answers the participant gives to the FPt stories with gaffes, the less errors he makes on the MCST. Moreover, FPt is a measure of Cognitive Empathy, while perseverative errors of MCST is an

interesting measure of EF, since it evaluates the incapacity of the participant to move from a rule to another after the suggestion of the examiner (Caraffa, 2004). The evidence that these two measures are related is in line with the aforementioned bound between ToM and EF (Russell, 1997; Carlson et al., 2002) and with the preliminary hypotheses of this study.

Finally, considering the relation between dystrophin mutation and cognitive abilities, we expected that BMD patients with distal mutations would perform worse relatively to BMD patients carrying proximal mutations on the neuropsychological evaluation. Actually, BMD patients carrying distal mutations performed worse relatively to BMD patients with proximal mutations on the DS_f test. As aforementioned, the DS_f test is a measure of Short-Term Memory capacity. It seems interesting that this test can distinguish BMD patients with proximal mutations from BMD subjects with distal mutations and it is also the test in which BMD patients outperformed controls. Probably this test is particularly relevant in delineating the cognitive profile of BMD patients. Anyhow, the worse performance of BMD patients with distal mutations relatively to patients with proximal mutations in this test confirm the evidenced of worse performance of BMD patients carrying mutations involving Dp140 isoform (Bardoni et al., 1999; D'Angelo et al., 2011) and the preliminary hypotheses.

8.3. FACIOSCAPULOHUMERAL DYSTROPHY

As regards patients affected by FSHD, according to the evidences emerged from literature, we expected a slightly worse performance of these patients relatively to the control sample in EFs tests and ToM tasks and, on the other hand, no differences between the two samples on Affective Empathy evaluation.

Effectively, FSHD patients showed a performance comparable to the one of healthy controls as regards EF. This result is in contrast with our preliminary hypotheses but, focusing on the evidences present in literature that highlight mild to moderate mental retardation primarily in patients with an early onset (Bindoff, 2006; Hobson et al., 2006), the outcome can be explained considering that all of the patients evaluated in this research expressed the first symptoms of the illness in the adult age, so the chance to find cognitive impairment, even if at a subclinical level, was further reduced.

As regards Empathy abilities, FSHD patients revealed a performance comparable to the one of healthy controls in most of the scores considered. Surprisingly, patients' scores in the Empathic Concern scale of IRI questionnaire and the total score of EQ questionnaire were significantly higher relatively to controls. The Empathic Concern scale, as aforementioned, assess "other-oriented" feelings of sympathy and concern for unfortunate others and is considered a measure predominantly related to Affective Empathy, while EQt is a questionnaire that, even if was not designed to discriminate between Cognitive and Affective Empathy, is more related to Cognitive Empathy. It's important to note that both these measures are self-report questionnaires in which the patients have to evaluate their own Empathy abilities.
As for BMD patients, it could be that FSHD patients, because of their debilitating illness that preserved their cognitive abilities and force them to cope with fatigue (Schipper et al., 2016), pain (Smith et al., 2014) and disease burden (Johnson et al., 2012), may develop finer empathic abilities as regards both the capacity to feel and share the emotions of other and the ability to understand the mental state of others.

Considering the aim of this study, the investigation of the relation between EFs and Empathic abilities, in FSHD patients it emerged a significant correlation between the TMT test and the scale Empathic Concern of IRI questionnaire. Another important correlation was found between the TMT test and the total score of the IRI questionnaire. The total score of TMT test provides information on visual search, scanning, speed of processing, mental flexibility, and EFs (Tombaugh, 2003). On the other side, while the Empathic Concern scale is more related to Affective Empathy evaluation, the total score of IRI questionnaire can be seen as a mixed measure, because the questionnaire is composed both by scales assessing more affective aspects of Empathy and questions principally related to Cognitive Empathy (Davis, 1980).
The fact that the results revealed that a measure of EF is related to a questionnaire assessing also Affective aspects of the Empathy construct is intriguing. It's important to remind that FSHD patients show gray matter loss in the anterior cingulate cortex (Quarantelli, 2006) and that the cortical areas that constitute the Cingulate Cortex result active in tasks assessing Affective Empathy (Vollm et al., 2006), in tests related to Cognitive Empathy (Gallagher and Frith, 2003), as well as in EFs' performance (Carter et al., 1998; Stroop, 1935; Dreher & Grafman, 2003).

Finally, we expected that FSHD patients with an EcoRI fragment size below 24Kb would perform worse in neuropsychological assessment relatively to FSHD patients with a fragment size over 24Kb. From data analyses it emerged that patients carrying a fragment size below 24Kb had a worse performance on the Fantasy Scale of IRI comparing to patients with a fragment size over 24Kb. The Fantasy Scale of IRI questionnaire is considered a subtest related to Cognitive Empathy and so can be seen as a score indicating a fine-grained measure of higher functioning. Considering the relation existing between Cognitive Empathy and EF, the evidences emerged from literature regarding the worse performance on cognitive assessment FSHD patients with a fragment size below 24Kb (Sistiaga et al., 2009) have been confirmed.

Surprisingly, the EcoRI fragment size correlated also with the total score of IRI questionnaire.
Also in this case, the performance of patients with a fragment size lower than 24Kb was worse relative to the performance of FSHD patients carrying a fragment size over 24Kb.
Considering that the IRI questionnaire is a generic self-report measure of Empathy and that the fragment size correlated also with one of the subscales that form this questionnaire, it's possible that the mild cognitive difficulties related to a low EcoRI fragment size have influenced negatively the answers given to this questionnaire.

8.4. X-LINKED SPINAL and BULBAR MUSCULAR ATROPHY

As regards patients affected by SBMA, in the light of the contrasting evidences present in literature, it has been carried out an explorative study with the aim to evaluate the EF of these patients considering larger samples of SBMA patients and controls.

In particular, considering the results emerged from the study of di Rosa et al. (2015) we expected a better performance of SBMA patients, relative to controls, in the Babcock story recall test, even if at a subclinical level.

Our sample of seventy individuals showed no impairment in any of the neuropsychological tests administered, when compared with those of healthy subjects matched for age and education.
No significant differences were found in Working Memory, Executive and attentional domains.

These results are clearly in contrast with most of the previous researches (Guidetti et al., 1996; Soukup et al., 2012; Yang et al., 2014; Kasper et al., 2014), but in line with the study of di Rosa et al. (2015).

It should be noted that in previous researches deficits were not striking and with some methodological issues.

For example, Guidetti et al. (1996) tested a whole family using neuropsychological tests assessing attention, logical functions, abstract thought, verbal fluency, visual spatial functioning, short term and long term memory. From this investigation emerged abnormal scores in affected patients primarily on the tests assessing long term memory and selective attention, specifically in prose memory, paired associated learning, supraspan spatial learning and the Stroop test. Even if long term memory and attention functioning have been examined as well, none of the tests proposed by Guidetti have been used in the present evaluation. In addition, most of our patients were not related to each other, apart from some rare pair of brothers or cousins.

Considering the study of Yang et al. (2014), it must be considered that the Authors tested patients and controls with MoCA scores well below the cut-off for cognitive impairment. The reason these results are so contrasting might be that usual testing is made to detect frank cognitive impairment, while with these individuals an assessment for more fine-grained abilities should suite better. An attempt in this direction has been made by Torralva et al. (2009), although in patients affected by fronto temporal dementia. Torralva found that tests tapping social cognition and Empathy discriminate better between patients and healthy controls, compared to classical testing. This example can give a hint on SBMA patients.

Considering neuroradiological evidence, literature indicates that hypometabolism is present in frontal cortical areas (Lai et al., 2013), but in this site there is no presence of mutant AR (Adachi et al., 2005). Other neuroimaging studies have found negative alterations of white matter and gray matter in the limbic system (Kassubek et al., 2007; Unrath et al., 2010). Therefore, the study of Di Rosa et al. (2015) showing no deficits in classical tests of memory and EFs, but revealing a deficit in Cognitive Empathy, might have discovered a better way to assess these patients.

As regards the performance on the Babcock story recall test, SBMA patients showed a better performance comparing to the control group. The Babcock Story test consists of a story with an emotional content (Babcock, 1930) because, as aforementioned, talks about a flood that caused dead, injured and sick. According to the Empathizing-Systemizing (ES) theory of Baron-Cohen

(2002), females show on average a stronger drive to empathize than males and one of the major factors determining sex-differences in Empathy has been suggested to be fetal testosterone (Chapman et al., 2006). Research indicates that women have a better memory for emotional information than men (Bloise et al., 2007), and that this information is rated as more arousing than males (Bremmer et al., 2000). These evidences, together with the known lower levels of testosterone in SBMA patients, could explain the results emerged from this research.

This increase of performance in the Babcock story test in SBMA patients can be explained also considering Paradoxical Functional Facilitation (PFF). PFF can be defined as the increase of the performance in a particular task in a context of a neurological disorder (Kapur, 1996) and commonly follow a direct or indirect brain damage. Even if it's known that psychological manipulations that results in PFF effects are rare (Kapur, 1996), this hypothesis can't be excluded.

Considering the impact that testosterone may have during the course of cognitive assessment (Lombardo et al., 2012) and the PFF hypothesis (Kapur, 1966), it has been investigated if the testosterone levels and PoliQ triplets' expression predicted the performance on Babcock story test as well as the other neuropsychological assessments. Unfortunately, regression analysis disconfirmed such hypothesis. Probably, the performance of SBMA patients on the Babcock story recall test and, more in general, in tasks assessing memory and related to emotional contents, needs deeper investigation to be explained adequately.

9. CONCLUSIONS

The research carried out on Empathy and EFs in NMD, with a particular focus on the relationship existing between these two fundamental construct, allowed us to highlight many aspects which to date had not yet been investigated.

The relation between Empathy and EFs emerged in all the NMD considered, even if not always as supposed: connections between EF and Cognitive Empathy were expected, considering the evidences from literature (Russell, 1997; Carlson et al., 2002). The unexpected results regarded the link between measures assessing Affective Empathy and tests assessing EFs, as showed in DMD and FSHD patients. The explanation of these results can be found considering the neural correlates that characterize these diseases and that are implicated in Affective Empathy tasks.

Other evidences regarding EF and the abilities related to Cognitive and Affective Empathy of the patients evaluated provided interesting elements. In particular, the DS_f task seemed to be particularly relevant in delineating the cognitive profile of BMD patients. Moreover, it emerged that both BMD and FSHD patients are particularly concerned about emotions and feeling of others compared to healthy participants.

The preliminary hypotheses have not always been met; on the other hand, the investigatory studies conducted, for example the neuropsychological evaluation of SBMA patients, allowed us to clarify the conflicting results reported in literature about this topic.

However, the study presents some limitations: considering the participants, it cannot be excluded the possibility of a bias in the selection of the patients: specifically, it can be that the patients that agreed to complete the evaluation protocol were more compliant and less severely impaired compared to the patients that refused to participate to the research.

Moreover, the evaluation protocols proposed in this study were created with the aim to be completed by the patients after the neurological evaluation; for this reason, the tests and questionnaires administered were restricted to the most relevant one. This choice may have affected the type of results that have been collected.

The findings emerged from this study can encourage several applications in clinical field. Know the Empathic abilities of patients affected by such debilitating diseases may be useful to clinicians in

order to create a good alliance. This issue is particularly relevant if we consider that a good patient-physician relation is necessary to cope adequately with the disease, also as regards compliance to treatments.

The presence of psychological support at the moment of the diagnosis and throughout the medical management would help patients to cope with the stress that these diseases lead and the consequences of these chronic and progressive illnesses. In addition, it could help caregivers to adapt to the daily new needs that the diseases require (Nereo et al., 2003).

Future research direction could be addressed to continue increasing the number of patients and control subjects involved in the research, as well as use additional tools that can examine in depth the aspects that in this first project were found to be relevant.

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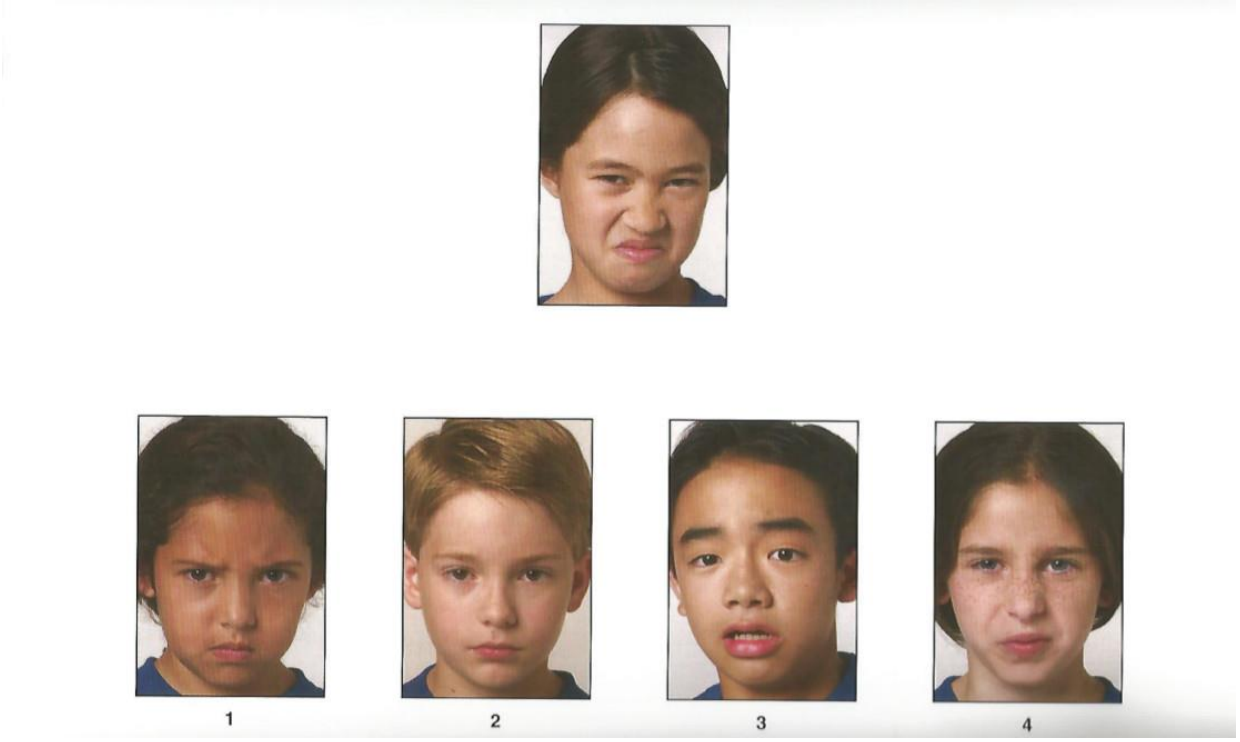
11.APPENDICES

APPENDIX I: example of the Contextual part of ToM test, NEPSY II

APPENDIX II: example of Affect Recognition test, NEPSY II



APPENDIX III: Faux Pas test, story with gaffes

2. Il marito di Elena le stava organizzando una festa di compleanno a sorpresa. Il marito invitò Sara, un'amica di Elena e le disse: "Non parlarne con nessuno, soprattutto con Elena." Il giorno prima della festa, Elena si trovava a casa di Sara quando Sara rovesciò un po' di caffè sul vestito nuovo appoggiato sulla sedia. "Oh!" esclamò Sara, "Volevo indossarlo per la tua festa!" "Quale festa?" domandò Elena. "Forza" disse Sara, "vediamo se riusciamo a lavare via la macchia."

Qualcuno ha detto qualcosa che non avrebbe dovuto dire o comunque qualcuno ha detto qualcosa di sconveniente?

Se sì, domanda:

Chi ha detto qualcosa che non avrebbe dovuto dire o comunque qualcosa di sconveniente?

Perché lui/lei non avrebbe dovuto dire quella cosa o Perché quella cosa è da considerarsi sconveniente?

Perché pensi che lui/lei abbia detto quella cosa?

Sara si ricordava che si trattava di una festa a sorpresa?

Come pensi che Elena si sia sentita?

Domande di controllo:

Nella storia, per chi era la festa di compleanno a sorpresa?

Che cosa è stato rovesciato sul vestito?

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APPENDIX IV: Faux Pas test, story without gaffes

1. Giulia era a una festa a casa del suo amico Antonio. Stava parlando con Antonio quando un'altra donna si avvicinò a loro. Era una delle vicine di casa di Antonio. La donna disse"Ciao," quindi rivolgendosi a Giulia aggiunse: "Non credo che ci siamo mai incontrate. Sono Maria, e tu come ti chiami?". "Giulia." "Gradite qualcosa da bere?" chiese Antonio.

Qualcuno ha detto qualcosa che non avrebbe dovuto dire o comunque qualcuno ha detto qualcosa di sconveniente?

Se sì, domanda:

Chi ha detto qualcosa che non avrebbe dovuto dire o comunque qualcosa di sconveniente?

Perché lui/lei non avrebbe dovuto dire quella cosa o Perché quella cosa è da considerarsi sconveniente?

Perché pensi che lui/lei abbia detto quella cosa?

Antonio sapeva che Giulia e Maria non si conoscevano?

Come pensi che Giulia si sia sentita?

Domande di controllo:

Nella storia dove si trovava Giulia?

Giulia e Maria si conoscevano?

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APPENDIX V: example of Reading the Mind in the Eyes Test

prova

invidioso

preso dal panico

arrogante

pieno di odio

APPENDIX VI: Interpersonal Reactivity Index

Interpersonal reactivity Index (IRI)

Le seguenti affermazioni indagano i suoi pensieri e sentimenti in situazioni diverse. Per ogni frase, le chiediamo di indicare il grado di accordo relativamente a ciascuna affermazione scegliendo il numero appropriata dalla scala all'inizio della pagina: 1, 2, 3, 4 o 5. Quando avrà deciso la sua risposta, scriva il numero vicino alla frase. LEGGA OGNI AFFERMAZIONE MOLTO ATTENTAMENTE PRIMA DI RISPONDERE. Risponda il più sinceramente possibile. Grazie.

SCALA DI RISPOSTA:

1 2 3 4 5
MAI VERO SEMPRE VERO

1. Sogno ad occhi aperti e fantastico, con una certa regolarità, sulle cose che potrebbero accadermi
2. Provo spesso sentimenti di tenerezza e preoccupazione per le persone meno fortunate di me
3. A volte trovo difficile vedere le cose dal punto di vista di un'altra persona
4. A volte non mi sento dispiaciuto per le altre persone che hanno problemi
5. Resto veramente coinvolto dagli stati d'animo dei protagonisti di un racconto
6. In situazioni d'emergenza, mi sento apprensivo e a disagio
7. Riesco solitamente ad essere obiettivo quando guardo un film o una rappresentazione teatrale e raramente mi lascio coinvolgere del tutto
8. In caso di disaccordo, cerco di tener conto del punto di vista di ognuno prima di prendere una decisione
9. Quando vedo qualcuno che viene sfruttato, provo sentimenti di protezione nei suoi confronti
10. A volte mi sento indifeso quando mi trovo in situazioni emotivamente molto coinvolgenti
11. A volte cerco di comprendere meglio i miei amici immaginando come le cose appaiono dalla loro prospettiva
12. Mi accade raramente di essere coinvolto da una buon libro o da un bel film
13. Quando vedo qualcuno farsi male, tendo a restare calmo
14. Le sventure delle altre persone a volte non mi turbano molto
15. Se sono sicuro di aver ragione riguardo a qualcosa, non spreco molto tempo ad ascoltare le argomentazioni degli altri
16. Dopo aver visto una rappresentazione teatrale o un film, mi sono sentito come se io stesso fossi uno dei protagonisti
17. Trovarmi in situazioni che provocano tensione emotiva mi spaventa
18. Quando vedo qualcuno che viene trattato ingiustamente, talvolta mi capita di non provare molta pietà per lui
19. Sono di solito piuttosto efficiente nel far fronte alle situazioni di emergenza
20. Le cose che accadono mi colpiscono molto spesso
21. Credo che esistano due opposti aspetti in ogni vicenda e cerco di prenderli in considerazione entrambi
22. Potrei descrivermi come una persone dal cuore piuttosto tenero
23. Quando guardo un buon film, riesco molto facilmente a mettermi nei panni di un personaggio principale
24. Tendo a perdere il controllo in casi di emergenza
25. Quando sono in contrasto con qualcuno, di solito cerco di "mettermi nei suoi panni" per un attimo
26. Quando leggo una storia o un racconto interessante, immagino come mi sentirei se gli avvenimenti della storia stessero accadendo a me
27. Quando vedo qualcuno che ha urgente bisogno d'aiuto in una situazione d'emergenza, crollo
28. Prima di criticare qualcuno, cerco di immaginare cosa proverei se fossi al posto suo

APPENDIX VII: Empathic Quotient

EQ Baron-Cohen Test (60items)

	ASSOLUTAMENTE D'ACCORDO	PARZIALMENTE D'ACCORDO	LEGGERMENTE IN DISACCORDO	ASSOLUTAMENTE CONTRARIO
1. Capisco con facilità se qualcuno vuole partecipare ad una conversazione.				
2. Preferisco gli animali agli esseri umani.				
3. Provo a seguire le nuove mode e le nuove tendenze.				
4. Quando un concetto per me facilmente intuibile non viene compreso alla prima spiegazione, ho difficoltà a rispiegarlo.				
5. Sogno la maggior parte delle notti.				
6. Prendermi cura degli altri è qualcosa che mi fa' veramente piacere.				
7. Provo a risolvere da solo i miei problemi piuttosto che discuterne con gli altri.				
8. Trovo difficile capire come comportarmi in mezzo alla gente.				
9. Sono al massimo della mia forma nelle prime ore della giornata.				
10. La gente mi dice spesso che insisto troppo sui miei argomenti.				

APPENDIX VIII: Babcok Story Test

TEST DI MEMORIA DI PROSA

Protocollo

"Sei / dicembre, / la scorsa settimana / un fiume/ straripò/ in una piccola/ città/ situata/ a 20 km/ da Torino/.
L'acqua/ invase/ le strade/ e le case/.
Quattordici/ persone/ annegarono/ e seicento/ si ammalarono/ a causa dell'umidità/ e del freddo/.
Nel tentativo di salvare/ un ragazzo/ un uomo/ si ferì/ le mani/ ".

Rievocazione immediata

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Rievocazione differita (dopo 10 min. dalla seconda lettura)

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Punteggio complessivo:

1° ripetizione	2°ripetizione	**totale**
…./8	…./8	**…./16**