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Electrophysiological Assessment of CNS Abnormalities in Muscular Dystrophy

Stefan M. Golaszewski and Raffaele Nardone

Abstract

Patients affected by muscular dystrophies often show CNS abnormalities. Patients with dystrophinopathies exhibit intellectual disabilities and mental retardation, while subjects with facioscapulohumeral muscular dystrophy (FSHD) often show epilepsy. Dystrophin and associated proteins have important roles in the CNS. Many patients with Duchenne and Becker muscular dystrophies (DMD/BMD) have cognitive impairment, learning disability, and variable degrees of mental retardation in addition to progressive muscular weakness. Unfortunately, the assessment of cortical function with TMS in DMD patients has not been able to delineate a clear picture and has yielded contradictory results. No TMS studies have been performed on BMD patients. Repetitive transcranial magnetic stimulation (rTMS) modulates cortical excitability, possibly by inducing a short-term increase in synaptic efficacy, and can be used to investigate motor cortex excitability in BMD patients. Changes in the size and threshold of motor evoked potentials (MEPs) and cortical silent period (CSP) duration evoked by rTMS delivered in 5 Hz trains of stimuli at suprathreshold intensity can be tested. Impaired muscular function might be partially compensated by an enhancement of motor excitability at the cortical level and/or at α -motoneuron level. TMS may thus offer a reliable means to characterize also important neurophysiologic and pathophysiologic aspects of cortical involvement in muscular dystrophy.

Keywords: transcranial magnetic stimulation, paired-pulse TMS, motor cortical excitability, myopathy, muscular dystrophy

1. Introduction

Muscular dystrophy (MD) is characterized by an absence or disruption of dystrophin and associated proteins with a severe pathology of the skeletal musculature with severe motor disabilities and even premature death of the individual. These proteins do not only have an important function within the skeletal musculature but also within the central nervous system. Thus, patients with muscular dystrophies often suffer from cognitive impairment, learning disability, and variable degrees of mental retardation in addition to progressive muscular weakness [1–3]. Patients with facioscapulohumeral muscular dystrophy (FSHD) are often affected by epilepsy [4, 5]. However, the pathogenetic role played by the absence or disruption of dystrophin on CNS function has not been clarified so far.

Transcranial magnetic stimulation (TMS) is a proper method to assess brain cortical excitability that is disturbed in muscular dystrophies. A TMS assessment of brain cortical function in DMD patients has yielded contradictory results [6]. While Yayla et al. reported no CNS abnormalities and similar motor threshold (MT) values in DMD patients and healthy controls, Di Lazzaro et al. reported a higher MT for magnetic than for electrical stimulation in four DMD patients [7]. Methodological reasons, as well as the small sample size of the latter study, may account for the discrepancies. Because repetitive TMS (rTMS) modulates cortical excitability, possibly by inducing a short-term increase in synaptic efficacy [8], rTMS can be used to investigate motor cortex excitability in humans. Changes in the size and threshold of motor evoked potentials (MEPs) and cortical silent period (CSP) duration evoked by rTMS delivered in 5 Hz trains of stimuli at supra-threshold intensity have been tested by Golaszewski et al. [9]. The main finding of this study was that 5 Hz-rTMS delivered in trains failed to elicit the normal MEP facilitation over the train in a group of Becker Muscular Dystrophy (BMD) patients with mental retardation or borderline mental retardation and BMD patients with normal intelligence and healthy controls did not show any abnormalities in 5 Hz-rTMS MEPs and CSPs. The lack of MEP facilitation in mentally retarded or borderline BMD patients during the 5 Hz-rTMS train of stimuli may thus reflect an altered short-term synaptic enhancement.

With the means of transcranial magnetic stimulation, important neurophysiologic and pathophysiological aspects of cortical involvement in myopathies can be detected [10, 11]. So far, a few studies applying TMS have detected abnormalities in cortical reactivity and plasticity in MD patients.

2. Electrophysiological markers in muscular dystrophy

2.1 Motor threshold

In a study of Di Lazzaro et al. in a small group of DMD patients and a control group (n = 4), the threshold for evoking MEPs using electrical anodal stimulation was the same. Otherwise, the resting motor threshold (RMT) for a stimulation with a circular magnetic coil at the vertex was higher in the DMD patients [7]. The higher threshold was interpreted as a reduced cortical excitability that may be related to an abnormal synaptic function due to the deficiency of brain synaptic dystrophin. However, in a study about the cortical excitability in Duchenne muscular dystrophy investigating central motor conduction time (CMCT), cortical silent periods, and paired-pulse TMS, there were no statistical differences between a group of DMD children and a group of age-matched control children except lower MEP amplitudes in the DMD children. Compared with a control group of healthy adults, the two children groups showed less short interval intracortical inhibition (SICI) and shorter CSP durations [6]. The difference between the two studies can be explained by the applied different methods, since in the study by Di Lazzaro et al., a circular coil was used and an unusual minimum stimulus intensity that evoked an EMG response of at least 100 μ V in 100% of 20 consecutive trials was the accepted resting motor threshold. Besides the small sample size in the study of Di Lazzaro et al. can be an explanation for the difference.

Oliveri et al. found that in patients with myotonic dystrophy, the stimulus threshold intensity did not differ between patients and healthy controls, but the mean cortical motor latency and CMCT were significantly prolonged in the patients compared to the controls. This can be interpreted as a central motor delay and a decreased excitability of motor neurons in the myotonic dystrophy patients [12].

In another study Di Lazzaro et al. [13] found that RMT was slightly increased in patients with FSHD as well as in patients with other muscle diseases such as limb-girdle muscle dystrophy (LGMD) and polymyositis [13]. However, Liepert et al. [14] could not show a significant difference in RMT between a group of patients with different myopathies (including FSHD, LGMD, emerinopathy, adhalinopathy, multicore disease) and a group of control subjects [14].

2.2 Central motor conduction time

As mentioned above Oliveri et al. investigated MEPs elicited by cortical and cervical magnetic stimulation in 10 patients with myotonic dystrophy. While MEP cervical latency, absolute or relative amplitude, and RMT did not differ significantly between patients and controls, the mean cortical motor latency and CMCT were significantly prolonged in the patients compared with 10 healthy controls [12]. This central motor delay can be explained by a decreased motoneuron excitability.

In several further studies, it was found that CMCT was normal in patients with FSHD and LGMD [13, 14] as well as in patients with DMD [6, 7].

2.3 MEP amplitudes/areas

Yayla et al. further described in his study [6] with DMD patients that mean MEP response amplitudes and areas, as well MEP/compound muscle action potential (CMAP) amplitude ratios, had a tendency to be lower than those of a control group, but only the differences in MEP area values reached a statistical significance [6]. An explanation for the reduced amplitude of CMAPs and MEPs could be the muscle damage in the DMD patients. Otherwise, DMD patients showed an increased ratio of the F-wave and the compound motor action potential (F/CMAP ratio), indicative for an increased α -motoneuron excitability. The mean F-wave amplitudes were not significantly different between DMD patients and controls. Therefore, the reason for a higher F/CMAP ratio in the DMD group is difficult to explain. One explanation may be an increased F-wave amplitude in the DMD patients that did not reach statistical significance especially due to their large variability. Another explanation may be the aforementioned low-amplitude CMAPs in DMD patients or an increased motor cortical excitability due to less SICI and shorter CSP durations in DMD patients with regard to healthy adult controls.

In the study of Liepert et al., MEP amplitudes of the first dorsal interosseous (FDI) and the deltoid muscle (DM) were increased in patients with different myopathies compared to controls [14]. The recruitment of a larger group of corticospinal neurons by the TMS pulses due to an increased motor cortical excitability with a consecutive increased activation of the α -motoneuron pool may explain this finding.

Finally, in the study of Oliveri et al., the first MEP study in patients with myotonic dystrophy, the mean MEP amplitudes did not differ between patients and controls [12].

2.4 Intracortical inhibition

In the study of Liepert et al. in myopathy patients with well-defined myopathies, the patients showed a reduction of SICI compared to an age-matched healthy control group [14]. This reduction of SICI was present in both clinically unaffected and affected muscles. In the patients, both MEP amplitudes and α -motoneuron excitability were enhanced, and, thus, it was concluded that excitability in myopathy patients was enhanced at cortical and subcortical levels in order to compensate for the muscle weakness or because of use-dependent plasticity. In all patients

irrespective of the type of myopathy, a reduced intracortical inhibition was found. Obviously, this neurobiological mechanism of increased motor cortical excitability for compensation of muscle weakness is independent of a particular muscle pathology in myopathies. However, with regard to the available electrophysiological data, there is no sufficient evidence to conclude that cortical disinhibition is a common feature of myopathies.

In 2004 Di Lazzaro et al. reported significantly reduced SICI in early-onset FSHD patients compared with patients suffering from other muscle diseases (LGMD and polymyositis) and healthy controls. Between polymyositis patients and controls, there was no significant difference in SICI [13].

2.5 TMS and fatigue

During fatiguing muscle exercise, a paired-pulse TMS paradigm can be applied to investigate the central inhibitory and excitatory mechanisms that occur at the motor cortical level. Paired-pulse TMS was already done in patients with multiple sclerosis and in healthy subjects [15, 16]. In a study of Schwenkreis et al., SICI has been applied prior to a fatiguing motor task, immediately post-exercise, and 40 minutes post-exercise in MD patients and patients suffering from fibromyalgia syndrome (FMS) [17]. In the MD and FMS patients, SICI was already reduced pre-exercise. Healthy subjects did not show any pre-exercise SICI decrease but a significant SICI decrease post-exercise. Thus, reduced SICI may be a central compensatory mechanism for peripheral or central fatigue. MD patients may use this neurobiological mechanism of reduced SICI already under baseline conditions, probably due to permanent muscle weakness. Probably due to a ceiling effect, the MD and FMS patients may not be able to further decrease cortical inhibition during the fatiguing exercise. This may be an additional central mechanism to the fatigue in MD and FMS patients. A fatigue syndrome belongs to the typical clinical feature of these patients.

An altered peripheral nerve excitability and reduced SICI at baseline in patients with MD type 1 (DM1) with impaired myoelectric properties (mean power frequency, muscle fiber conduction velocity) have been demonstrated in a study of Boerio et al. [18]. The remaining excitability parameters did not vary post-exercise in patients in contrast to the healthy controls.

In patients with colchicine myopathy with reported fatigue but no significant muscle weakness, Lin et al. investigated central compensatory mechanisms [19]. The patient and control group did not differ in the results. Obviously, there is no change in motor cortical excitability in acquired myopathy due to colchicine, while central reorganization may occur in patients with hereditary myopathy to compensate for muscle weakness.

2.6 Cortical plasticity

Repetitive TMS has also been applied to investigate motor cortex plasticity in patients with Becker muscular dystrophy [9]. The rTMS-induced facilitation of MEPs was significantly reduced in mentally retarded or borderline mentally retarded classified BMD patients when compared with BMD patients with normal intelligence and age-matched healthy controls (see **Figure 1a**). The increase in the duration of the cortical silent periods was similar in both patient groups and controls (see **Figure 1b**). These findings suggest an altered cortical short-term synaptic plasticity in glutamate-dependent excitatory circuits within the motor cortex in BMD patients with intellectual disabilities.

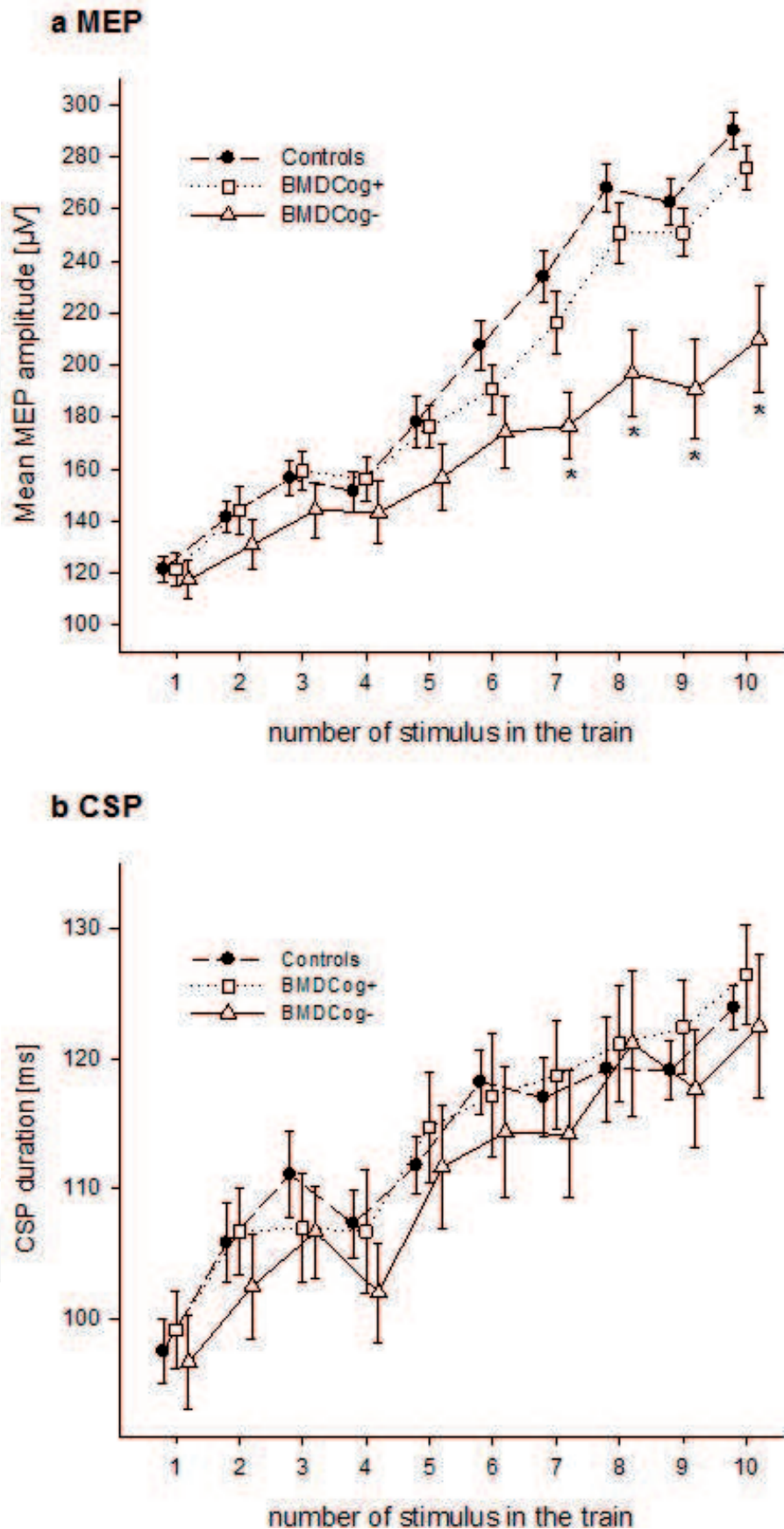


Figure 1. (a and b) Changes in the size of motor evoked potentials (a) and in the duration of cortical silent period (b) in the FDI muscle during repetitive transcranial magnetic stimulation trains of 10 pulses delivered at 5 Hz in the 6 patients with Becker muscular dystrophy and mental retardation or borderline (BMD-Cog-), the 7 patients with BMD and normal intelligence (BMD-Cog+), and the 10 age-matched healthy subjects (controls). Data are expressed as mean \pm SE. Asterisks indicate significant differences ($p < 0.05$, Bonferroni adjusted) between patients and controls.

3. Discussion

The studies reviewed here show that most TMS measurements vary considerably from study to study. The cause of this variability remains unclear, but the methodological problem of TMS and technical factors, including the relatively small sample size in most studies or the difficulty of many patients (especially children) to achieve complete muscle relaxation, can explain this variability. Several TMS studies have provided electrophysiological evidence for abnormal motor cortical excitability and/or plasticity in patients with different myopathies. Applications of TMS to characterize musculoskeletal pathophysiology in patients with myopathies appear to be safe and can be developed in valuable biomarkers.

In a first study of patients with MD, TMS has been reported to have subclinical central motor conduction abnormalities suggesting that the integrity of the corticospinal tract is also affected. This deficiency was considered one of the multisystem manifestations of muscle disease, regardless of muscle pathology [12]. However, these preliminary results were not confirmed by successive studies in other myopathies.

The reviewed TMS studies showed that it is possible to detect changes in motor cortex excitability in myopathy patients. The most important finding is a significant reduction in SICI compared to healthy controls.

In adult patients with various types of myopathies, including FSHD and LGMD, the mechanisms of intracortical inhibition are reduced. This finding has been interpreted as a compensatory mechanism within the central nervous system that helps patients with myopathy to regain muscle power. SICI deficiency in FSHD may be explained by overexpression of the gene encoding the diazepam binding inhibitor (DBI), which is expected to attenuate the effects of GABA on GABA_A receptors by acting on the benzodiazepine binding site [20]. Thus, DBI can determine a reduction in SICI, a phenomenon that depends largely on intracortical GABA_A inhibitory mechanisms. It is interesting to note that a decrease in initial intracortical inhibition may prevent the subsequent use of this compensatory mechanism within the central nervous system in fatiguing muscle exercises as can be seen in healthy subjects [17]. Reduced baseline SICI in MD can be considered compensatory because of peripheral weakness, whereas in fibromyalgia syndrome, reduced SICI should rather be considered as an indicator of primary central disinhibition. Also in DM1 patients, TMS revealed abnormalities in cortical excitability, thus suggesting the occurrence of intracortical dysfunction [18]. These results are consistent with the autopsy and neuroimaging studies showing that dysfunction of the brain can be accompanied by structural changes. As a result, a disturbance of neuronal architecture was detected in the autopsy of the brain [21]. In addition, a three-dimensional magnetic resonance imaging-controlled study demonstrated cerebral parenchymatopathy and hyperintensive lesions of the white matter [22], and PET scans showed a hypoperfusion in the prefrontal, temporal, and parieto-occipital lobes as well as in the basal ganglia, supporting the hypothesis of brain dysfunction in patients with DM1 [23].

In DM1 patients reduced intracortical facilitatory mechanisms (ICF) were found too [18]. Further, CNS excitability properties were markedly altered at the baseline and were not prone to be further impaired after a fatiguing exercise. Adjusting the cortical and neuromuscular features to the initial change may prevent increased fatigue after exercise performed with a maximum voluntary contraction percentage. The authors hypothesized that fatigue in MD patients may be mainly due to peripheral factors related to muscle pathology. Thus, MD patients were probably unable to reach the required force level of 50% of their maximal grip force for enough time to determine a reduction of corticospinal excitability, a marker of

central fatigue [24]. This may explain the lack of reduced MEP amplitudes after fatiguing exercise in these patients.

It is interesting to note that central compensatory mechanisms can be observed in patients with hereditary myopathies, whereas a single study on TMS in an acquired colchicine myopathies showed normal corticospinal excitability.

Many patients with dystrophinopathies (DMD and BMD) also suffer from cognitive impairment, learning difficulties, and variable mental retardation in addition to progressive muscle weakness [1–3]. The role played by the absence or disruption of dystrophin within the central nervous system is unclear, and the pathogenic conditions leading to mental retardation in MD patients are still unknown. TMS investigation of cortical function in DMD patients did not delineate a clear picture of motor cortical abnormalities and led even to contradictory results. Yayla et al. did not report any motor cortical abnormalities [6], and Di Lazzaro et al. reported higher MT for magnetic than for electrical stimulation in four DMD patients [7]. As already discussed, methodological reasons, as well as the small sample size of the latter study, may account for these discrepancies.

During 5 Hz-rTMS in BMD patients, MEP facilitation as observed in healthy subjects was reduced in contrast to the above-reported study of Yayla et al. [6, 9]. 5 Hz-rTMS MEP facilitation reflects mechanisms of short-term plasticity within the motor cortex that probably differ from those involved in the paired-pulse TMS facilitation and are likely related to an enhancement in the activity of I-wave generating circuits [25]. Intracortical facilitation in paired-pulse TMS is a complex phenomenon reflecting the activity of still poorly defined cortical circuits independent from those involved in I-wave generation [26].

The results of the study of Golaszewski et al. indicate impaired cortical plasticity in glutamate-dependent excitation circuits in mentally retarded BMD patients consistent with the results of several experimental studies indicating abnormal glutamatergic transmission in muscle diseases caused by mutations within the dystrophin-encoding gene [9]. In particular, the product of the dystrophin gene, dystrophin-71, in glutamate receptor signaling and possibly clustering, appears to be involved [27]. Besides, dystrophin-deficient mdx mice are more resistant to kainic acid-induced seizures but not to GABA antagonist-induced seizures compared with control mice. In the mdx mice, the kainic acid receptor density in the brain was found to be significantly lower than in the control mice, although the density of muscarinic cholinergic receptors, another important neurotransmitter receptor for cognitive function, was normal. The disruption of the dystrophin complex may lead to an instability of kainate-type glutamate receptors on the synaptic membranes with resulting inefficient neurotransmission in DMD patients [28].

It is important to note that the rTMS approach cannot be used to study cortical plasticity in children with DMD because the safety guidelines for the TMS application have been updated in the research and clinical environments [29]. The updated guidelines recommend that children should not be used as subjects for rTMS without compelling clinical reasons. Alternatively, the paired associative stimulation (PAS) technique can be applied in MD children that provide information about different aspects of cortical plasticity. So far, PAS has not yet been applied in myopathy patients and MD children [30]. No study has measured cortical responsiveness or plasticity outside the motor cortex.

Integrated approaches using TMS in conjunction with high-density EEG may reveal altered cortical plasticity and functional connectivity across different neuronal networks, similar to several other neurological and psychiatric disorders.

TMS can also affect brain function during repeated administration. rTMS can modulate cortical excitability and induce long-lasting neuroplastic changes [31, 32]. rTMS has been used for therapeutic purposes in patients with many neurological

and psychiatric disorders because it can induce long-term modulation of brain activity in the target brain region and across brain networks via transcranial induction of electrical currents in the brain. rTMS involves mechanisms of synaptic plasticity, and, recently, an association between rTMS-induced aftereffects and the induction of synaptic plasticity has been demonstrated [33]. Since abnormal cortical excitability and neuroplastic changes may play a role in the clinical expression of myopathies (including muscle weakness and fatigue), their modulation by rTMS may have a therapeutic potential. If the abovementioned changes affect motor control, treatment, or rehabilitation, strategies based on these abnormalities can help to improve the outcome of myopathy patients in neurorehabilitation.

In summary, only a few studies have used TMS for the electrophysiological characterization of cortical involvement in neuromuscular diseases. However, TMS may be promising as an electrophysiological biomarker in patients with muscular dystrophy and other myopathies, in identifying potential therapeutic targets and in monitoring the effects of suspected pharmacological applications. Neuromodulation by rTMS may have a therapeutic potential in the future to induce synaptic plasticity as a compensatory neurobiological mechanism for progressive muscle weakness to improve treatment outcome.

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