**Title:** Short-term neuromuscular electrical stimulation training of the tibialis anterior did not improve strength and motor function in facioscapulohumeral muscular dystrophy patients

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## ABSTRACT

Objective: To investigate the effects on motor function, muscle strength and endurance of short term neuromuscular electrical stimulation (NMES) training of the *tibialis anterior* (TA) muscles in patients with facioscapulohumeral muscular dystrophy type 1 (FSHD1) in comparison with healthy controls.

Design: This prospective study included ten patients with FSHD1 and ten healthy participants (HP). Maximal voluntary isometric contraction (MVC) of ankle dorsiflexion (DF) and a 2-minute sustained DF MVC with surface electromyography recordings (sEMG) of the TA and the soleus muscles were measured and motor function clinical tests were performed before and after the training period.

Results: No significant short term training effect was found in any of the investigated variables for either group, although a tendency towards an increase was noted for the manual muscle testing of the FSHD1. Patients with FSHD1 showed lower MVC force and lower maximal TA sEMG amplitude than HP. During the 2-minute sustained MVC, the percentage of force loss was lower for the FSHD1 patients, suggesting that they were experiencing a lower amount of muscle fatigue compared to the HP group.

Conclusion: The present NMES protocol was not strenuous enough and/or the parameters of stimulation were not adequate to improve dorsiflexion strength, muscle endurance and motor function in FSHD1 patients and HP.

**KEY WORDS**: Isometric strength; Muscle endurance; Electromyography; Neuromuscular disorder

## INTRODUCTION

With a European prevalence of 4/100,000, the facioscapulohumeral muscular dystrophy (FSHD) is the most common inherited muscular dystrophy disease. The FSHD is genetically heterogeneous and two types of FSHD (*i.e.,* FSHD1, 95% of patients and FSHD2, 5% of patients) have been identified.[1] Independently of the type of FSHD (*i.e.,* 1 or 2), the disease is characterized by a progressive asymmetric muscle weakness and atrophy usually spreading form facial to shoulder girdle, arms, abdominal and lower limb muscles.[2] In addition to muscle weakness, fatigue and pain are the two other most frequently reported symptoms. In particular, severe fatigue, a major burden in daily life activities, is reported by 61% of patients with FSHD [3] conducting to a sedentary lifestyle through a reduced level of physical activity.[4] The reduced level of muscle strength has been identified as a key factor in explaining low level of physical activity and high experienced fatigue.[5] In patients with FSHD1, *tibialis anterior* muscles can be affected in earlier stages of the disease than other lower limb muscles [6,7] and this decline in *tibialis anterior* function is frequently considered as the first disabling symptom.[8] Since the *tibialis anterior* has a strong functional role in gait and balance, both its weakness and fatigue may lead to a loss of mobility and increase the risk of falling.[4] Since no therapeutic treatments are yet available for FSHD,[2] it is of interest to propose alternative procedures to moderate the progressive loss of strength, endurance and muscle function.

Aerobic exercises have been proposed to improve muscle function in patients with FSHD, but some studies failed to show improvements on strength of such training, even though no deleterious effects were reported.[9,10] Neuromuscular electrical stimulation (NMES) is another type of exercise broadly used in rehabilitation settings.[11] When NMES training was performed on patients suffering from disabling forms of muscular dystrophy, such as Duchenne and Becker dystrophies, tolerance and efficacy were shown to maintain or even improve muscle strength.[12–15] Comparable results in the *tibialis anterior* and the quadriceps muscles were

reported in a group of mixed patients with neuromuscular disorders including patients with FSHD.[16] More recently, NMES training, performed on shoulder girdle and knee extensor muscles, was found to be safe and effective in improving strength and muscle function in patients with FSHD1.[17] The two studies that have investigated the NMES training programs in FSHD[16,17] involved long training periods of 14 and 5 months respectively. Although beneficial effects of short term (less than 8 weeks) NMES training programs on muscle strength and/or endurance in healthy participants[18,19] or patients with muscular dystrophy[12] were found, such programs have not been implemented in patients with FSHD. Therefore, the objective of this study was to investigate the effect of a bilateral 8-week NMES training on the *tibialis anterior* muscle in adults with FSHD1. It was hypothesized to observe muscle strength and endurance gains in dorsiflexion as well as improved motor function in patients with FSHD1.

## METHODS

### Participants

Ten adults with FSHD1 (mean ± standard deviation (SD): 5 females and 5 males; age 62.3 ± 10.2 year; height: 168.5 ± 12.8 cm; body mass: 73.7 ± 15.2 kg) and 10 healthy participants (HP) age matched (7 females and 3 males; age 56 ± 4.8 year; height: 171.5 ± 9.01 cm; body mass: 74.8 ± 12.4 kg) volunteered to take part in the study and written informed consent was obtained from all participants. The study was carried out according to the Declaration of Helsinki and approved by the local Institutional Human Ethics Committee (CPP10.067). The trial was declared (NCT00821548).

Adults patients diagnosed with FSHD1 were recruited from the outpatient record of the physical medicine and rehabilitation department at the hospital and were included into the

study according to the following criteria: number of 4q35 D4Z4 <11 repeats (mean of the group 6.89 ± 1.37 units), no mutation on *SMCHD1* gene ; muscle weakness of ankle dorsiflexion from 2 to 4 at least on one leg, assessed by manual muscle testing (MMT).[20] Exclusion criteria comprised previous NMES training of the lower-limb; history of cancer, joints pathologies, or collagenopathies, parturient, or breast-feeding woman or simultaneous participation to another research study.

**Neuromuscular electrical stimulation training**

Bilateral neuromuscular electrical stimulation (NMES) training sessions of the *tibialis anterior* muscles were performed with a Compex (Rehab 400, Cefar-Compex, DJO France SAS, Mouguerre, France) portable battery-powered stimulator. Participants either exercised at home or were trained by one of the experimenters or a physiotherapist. All healthy participants as well as four patients with FSHD1 carried out their training sessions at home. In the case participants trained at home, a weekly appointment was set-up with one of the experimenters to provide feedback and to control the quality of the training. During these training sessions participants were seated (hips, knees and ankles angles at 90°) with their feet fixed. During the training sessions, the participants were instructed to place comfortably their feet under a heavy-weighted object so that the feet would be firmly stuck and would not move during the contractions. The participants were simultaneously stimulated bilaterally with self-adhesive electrodes (2 mm thick) made of elastomer (5 cm x 5 cm) that were positioned as follows: the positive electrode was placed on the superior part of the muscle, whereas the negative electrode was placed on the medial part of the muscle, over the muscle bulk.

The NMES training program lasted for 8 weeks, with 3 sessions a week. Each session was composed of a 2-minute warm-up, followed by the 20-minute working out session, and finishing with 3 minutes of relaxation. The NMES program consisted in isometric

contractions of 9s (rise time: 1.5s; steady tetanic stimulation time: 6s; fall time: 1.5s) followed by a pause lasting 7 seconds (duty cycle: 56.25%) at 35 Hz and with a 200µs pulse-width. These stimulation parameters were chosen accordingly to previous successful NMES using low-frequency protocols in patients with neuromuscular disorders to increase muscle strength. [12–17] Participants were encouraged to increase stimulation intensity progressively every 5 minutes throughout each session up to individual tolerance threshold (i.e., discomfort/pain) since strength gains would be dependent on the stimulation intensity.[21,22] As individual tolerance threshold varied among participants, they were instructed to increase progressively stimulation intensity during the warm-up period to ensure a visible muscle contraction. However, since the feet were secured, no joint movement was induced. Moreover, during each of the training sessions, the participants or the physiotherapist, according to the training modality (i.e., supervised or at home) had to fill-out a questionnaire consisting in reporting the following: date and time of the training session; the mean intensity of the neuromuscular electrical stimulation delivered; self-evaluation of their perceived fatigue after the training session; the discomfort related to the NMES delivered during training sessions. Visual analogue scales (VAS) were used to score perceived fatigue and discomfort. A score of 0 mm indicated no fatigue or no discomfort and 100 mm indicated unbearable fatigue or maximum discomfort.

**Study design**

To disclose the effect of the 8-week NMES training, at pre and post training, the participants had first a blood sample collection, followed by a clinical examination and neuromuscular tests. Following this, they answered a questionnaire during a 30 min period of rest and then performed a 6-min walk test (6MWT).

*Blood samples collection*

To establish tolerance to NMES training, Plasma Creatine Kinase (CK) was measured after the fourth week (W4), and once randomly during the training in addition to before and after the 8-week training period (W8). Blood samples were collected and analyzed at the hospital. The first and last CK measurements were determined at rest, whereas the 4-week and the random test were performed within two hours following the NMES training. Plasma CK activity was determined spectrophotometrically by an automatic analyzer using a test kit (Roche/Hitachi Automated Clinical Chemistry Analyzer, Modular P-800, Roche Diagnostics, Meylan, France). The CK activity was considered as a biological marker of training-induced damage for each participant.

*Clinical examination*

Muscle function and strength of the TA were assessed manually by a physiotherapist, by manual muscle testing - MMT.[20] Depending on the amplitude of the ankle dorsiflexion, without extension of the hallux, scores were ranked from 0 where the muscle is no longer capable of force production to 5 representing the absence of muscle impairment.

The Motor Function Measurement (MFM) assessed the functional capacity of daily life activities: standing still, weight transfers, sitting, proximal and distal motor ability of muscles, walking, standing up, raising up arms, stepping up stairs, brush hairs *etc*. After evaluation, the total score was presented as a percentage, with healthy participants reaching 100%.[23] The physiotherapist performing the clinical examination was experienced to assess patients suffering from neuromuscular disorders and was not blinded to the evaluation.

*Neuromuscular tests*

Maximal voluntary contractions (MVC) of the dorsiflexor muscles were carried out unilaterally in a custom made device [24] consisting of a fixed footplate, where the foot was firmly strapped to avoid any movement and ensure the quality of the isometric force measurement. A strain-gauged transducer (model OMF06M, linear range 0-15 kN, precision ± 0.5 %, sensitivity 10 mV/kN; OMICRO'N, Gambais, France) was placed on the footplate to measure force production. During all contractions, the participants were seated on a chair, with their knee slightly flexed according to the comfort of the participant. The foot was firmly tightened with belts over the footplate with an ankle angle of 90°. The participants were not constrained and were allowed to seat as comfortably as they could, however, during MVCs, they were not allowed to hold the seat and were asked to remain as steady as they could.

Bipolar surface electromyography (sEMG) electrodes (10 mm diameter, 20 mm inter-electrode distance) recorded the electrical activity of the tibialis anterior (TA) and the soleus (SOL) muscles. The reference electrode was placed on the bony part of the contralateral patella. Skin was cleaned and abraded prior to the placement of electrodes, and low resistance impedance between electrodes (<5 kΩ) was obtained. A Biopac MP 150 system (Biopac systems, Inc., Holliston, MA, USA) was used to record sEMG data at a sampling rate of 2000 Hz. Electromyographic signals were amplified with a bandwidth frequency ranging from 1 Hz to 500 Hz (common mode rejection ratio = 11 dB; impedance input = 1000 MV; gain = 1000).

The tests were performed on both legs, one at a time, in a random order with at least 10 minutes of rest period between each leg. Two MVCs of dorsiflexion were performed on each leg to determine the maximal strength production and the concomitant sEMG signals of both the TA and the SOL muscles. A 60-second rest was allowed between each contraction. Then, a fatiguing task consisting of an isometric 2-minute MVC [25] of dorsiflexion was performed with recordings of the sEMG of TA and SOL muscles. No visual feedback was provided to

the participants and they were asked to perform an all-out effort while they received strong verbal encouragement.

*Questionnaire and 6-min walk test*

Quality of life of the participants was evaluated with the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire.[26] A 6-min walk test (6MWT) was used to assess the greatest distance participants could walk in 6 minutes on a 20-meter shuttle.

**Data analysis**

The MVC was considered as the mean value over a 500-ms period around the peak force. The best of the two trials was analyzed. During the fatiguing task, the percentage of MVC loss was calculated as the difference of a 1-second window width at the start and a 1-second window width at the end of the 2-minute MVCs. All sEMG data were analyzed over the same window width as the force data where the root mean square (RMS) of the TA and the SOL (TA RMS and SOL RMS) was quantified and the loss in TA RMS was computed. RMS was calculated with commercially available software (AcqKnowledge 4.1, Biopac Systems, Inc., Holliston, MA, USA), while the rest of the outcome measures were analyzed with Matlab R2010b (The MathWorks, Inc., Natick, MA, United-States).

**Statistical analysis**

Statistical processing was performed using Statistica® software for Microsoft Windows (StatSoft, version 8.0, Tulsa, OK, USA). The Shapiro-Wilk test was used to test whether outcome measures were normally distributed, and depending on the results the appropriate statistical test was performed. When data were normally distributed, an unpaired Student t-test was performed to compare FSHD1 and HP groups and a paired Student t-test was used to disclose training-induced changes within group (FSHD1 and HP). When data did not follow a normal distribution, equivalent non-parametric tests, the Mann-Whitney *U* test and the Wilcoxon signed ranks test were performed. A two-way ANOVA (leg × time) with repeated measures on time was performed on the intensity values recorded during each training session, while the Friedman ANOVA was applied for the discomfort and fatigue VAS values as they did not follow a normal distribution. In all statistical analysis the significance level was set at $p<0.05$. Unless specified, normal distributed data are expressed as means ± SD (standard deviation of the mean), in the entire manuscript and in the tables and figures, while

non-normally distributed data are expressed as median ± IQR (inter quartile range) in tables and box-plots are used in figures.

## RESULTS

### FSHD1 patients and healthy participants before the training period

The plasma CK concentration was higher in FSHD1 patients before the training period (t=4.38; $p<0.001$; Table 1). The MMT (Right: U=5.0; $p<0.001$; Left: U=0.0; $p<0.001$;) and MFM scores of the FSHD1 patients were significantly impaired compared to the HP before the training period (U=0.0; $p<0.001$; Table 1). Similarly, the distance covered during the 6MWT by the FSHD1 patients was shorter compared to the HP (t=-2.63; $p=0.02$; Table 1). Lastly, quality of life assessed by means of SF-36 questionnaire (Table 2) revealed lower values of FSHD1 patients compared to the HP for the following subscores: physical functioning (U=6.5; $p<0.001$), social functioning (U=18.0; $p<0.05$), vitality (U=14.5; $p<0.05$), general health (U=5.0; $p<0.001$) and the standardized physical component (U=7.0; $p<0.01$).

*Neuromuscular tests and fatiguing task*

As illustrated in the Figure 1A, the peak force during ankle dorsiflexion MVC was significantly lower in FSHD patients than in HP prior to the training period for both legs (Right, Pre: U=88.0; $p<0.001$; Left, Pre: U=102.0; $p<0.001$). The associated amplitude of the TA RMS during dorsiflexion MVC (Figure 1B) was lower in the FSHD1 patients compared to the HP before (Right: U=95.0; $p<0.001$; Left: U=90.0; $p=0.013$) the training period. In addition, the amplitude of the SOL RMS during dorsiflexion MVC was found lower in the FSHD1 patients before on the right leg (U=85.0; $p=0.007$), but not on the left leg ($p=0.282$). Although not significantly different for the left leg ($p=0.095$), the group of patients with FSHD1 exhibited a lower force reduction during the 2-minute MVC than the HP group before

the training period on the right leg (Right: U=10.0; $p$=0.003; Figure 2A). No difference in percentage of TA RMS and SOL RMS reduction between groups was found before the training period for either leg ($p$>0.05).

**Effects of NMES training in FSHD1 patients and healthy participants**

Individual patient/healthy participant's compliance to the training program was maximal (i.e., 100% of the scheduled training sessions attended). Whatever the group considered, plasma CK did not change significantly during the NMES training period ($p$>0.05). The NMES training did not modify the SF-36 questionnaire subscores and the values of the FSHD1 patients remained lower than those of the HP (Table 2). Also, no significant changes of the MFM and 6MWT assessments were observed after the training period ($p$>0.05) and the values of the FSHD1 patients remained lower than those of the HP (Table 1). Although no significant differences were found, the MMT values of the FSHD1 patients tended to slightly increase after the training period ($p$=0.067; Figure 3) for both the right and left legs. Also, when considering exclusively legs (i.e., fourteen legs) matching the inclusion criterion of having a MMT score of ankle dorsiflexion comprised between 2 to 4, a significant training effect was observed ($p$=0.027; data not illustrated).

*Neuromuscular tests and fatiguing task*

No significant training effect was found in dorsiflexion strength ($p$>0.05; Figure 1A) and in the associated RMS amplitude of the TA ($p$>0.05; Figure 1B) and the SOL muscles in either group for both sides. All these variables of the FSHD1 patients remained lower than those of the HP (Figures 1 and 2).

The force reduction during the 2-minute MVC did not changed after the training period for both legs in the FSHD1 patients and HP ($p$>0.05; Figure 2A). Although no significant

difference was found for the left leg, the TA RMS reduction of the right leg during the 2-minute MVC was significantly greater after the training period for the FSHD1 patients (t=3.33; $p>0.05$; Figure 2B). No significant change was noted for the HP. Also, no change of the SOL RMS reduction was found after the training period for either leg or group.

*Characteristics of the NMES training program*

As illustrated in the Figure 4, the stimulation intensity of the NMES training was significantly increased for the FSHD1 groups on both legs (F=1.89; $p<0.05$) as well as for the HP (F=3.26; $p<0.001$). The self-reported evaluation of the discomfort level throughout the training reduced on the right leg only in the group of patients with FSHD1 ($\chi^2$=36.1; $p$=0.041; Left leg: $\chi^2$=28.2; $p$=0.208), whereas no change was observed for the group of healthy participants ($p>0.05$). Likewise, the self-reported fatigue level reduced significantly in the group of patients with FSHD1 along the training only in the left leg (Left leg: $\chi^2$=40.3; $p$=0.014; Right leg: $\chi^2$=34.3; $p$=0.061). No change was observed for either leg in the HP group ($p>0.05$).

## DISCUSSION

The purpose of this study was to investigate whether a short term bilateral NMES training on the *tibialis anterior* muscles in adults with FSHD1 would be well tolerated and would improve muscle strength, endurance and motor function. All participants completed the 8-week NMES training program and no side effects were reported during or after the training period. Unfortunately, this program did not improve ankle dorsiflexion maximal muscle strength, nor muscle endurance or motor function in patients with FSHD1, although a tendency towards an increase was observed for the MMT scores. Also, no significant improvements were noted for the healthy participants.

All the participants (*i.e.,* FSHD1 patients and HP) completed the NMES training program and according to the CK measurements, no rhabdomyolysis was induced by the NMES protocol. Also, discomfort and fatigue VAS values reported throughout the protocol remained clinically low (mean VAS<2) and did not significantly increase during the 8-week period. These results agree with previous studies investigating the effects of NMES training programs in neuromuscular diseases[17] and confirm that NMES exercise is well tolerated by FSHD1 patients and HP.

Although well tolerated, this study failed to show a positive significant effect of NMES on muscle strength, muscle endurance and motor function of the ankle dorsiflexor muscles in FSHD1 patients, as well as in the HP. These observations are somehow surprising considering that benefits of NMES training programs on muscle strength are widely reported in literature for similar, or even shorter training periods in healthy participants [18,19]. In addition, the use of NMES was shown to be effective in patients with muscular dystrophies [12–15] and in patients with FSHD1.[16,17]

Although, the characteristics of stimulation parameters used here (35 Hz of frequency and 200-µs pulse duration) may be questioned, these NMES parameters were chosen since they were successfully used in previous rehabilitation settings in patients with muscular dystrophies.[13,17] However, FSHD1 patients can have fat infiltration in TA muscles [6,27] and strong alteration of the sarcomeric contractile properties, preferentially of type II fibers,[28,1] reducing the overall capacity of the muscle to contract. Nevertheless, this reason cannot account for the absence of improvements in the HP. Considering that frequencies above 50 Hz are suggested to maximize the training effect of NMES on muscle strength in healthy participants,[22] it may be suggested that these frequencies should be considered in future NMES studies in FSHD1 patients.

The lack of significant improvements could also be attributable to the frequency of the sessions and/or the duration of the training. Only three sessions per week for eight weeks were performed, whereas Colson et al.[17] trained their FSHD1 patients five days per week over a 5-month training period. Similarly, Milner-Brown and Miller[16] obtained significant improvement in strength after a 2-hour session performed 5 days per week during 14 months. Therefore, a higher volume training period (greater number of sessions or duration) might be required to obtained significant strength improvements in FSHD1 patients. Finally, as previously suggested, the stimulation intensity was constantly increased throughout the training period to ensure strength adaptations.[22] However, this stimulation intensity increment might have been too moderate to improve muscle strength. Therefore, it seems that the main reason for the absence of strength increase in FSHD1 patients has to be related to the frequency and/volume of the NMES sessions. Moreover, in the FSHD1 patients, the impaired muscle function of the TA at the beginning of the study can be suggested as a possible reason candidate for the training to be ineffective. Since no training effect was seen in the HP group either, this cannot be stated with certitude. Finally, the *soleus* muscle activity of the right leg during the dorsiflexion was found to be of lower magnitude compared to the left leg for the FSHD1 patients before the training. This observation confirms that important imbalance exits between limbs (i.e., asymmetric muscle weakness) and that particular neuromuscular adjustments/compensations could occur with the disease in order to maintain functional movements. These neuromuscular imbalances and their influence on functional daily tasks such as balance/walking should be further investigated in FSHD patients.

Interestingly and although it did not change with the training period, the MVC loss was much lower in the FSHD1 patients than in the HP during the 2-minute fatiguing task. This may indicate that patients with FSHD1 experienced a lower amount of muscle fatigue compared to the HP,[25] before and after the training, likely for several reasons. First, as the amplitude of the

TA EMG RMS reduced similarly, this suggests that the neural drive to the muscles would have become suboptimal with fatigue for both groups in the same fashion during the fatiguing exercise.[29] Second, patients with FSHD1 have strong alteration of the sarcomeric contractile properties of type II fibers,[1,28] which could lead to muscles more resistant to fatigue. Third, weaker participants are shown to be less fatigable than stronger ones,[30] as the intramuscular pressure is lower the negative feedback from afferent groups III and IV is therefore diminished.[30] Even though, the group of patients with FSHD1 showed a greater TA EMG RMS loss after the training in comparison to the loss before the training, this decrease was similar in both groups. Since the patients group showed lower force losses, it can be suggested that at the task truncation, the group of patients with FSHD were experiencing a lower amount of muscle fatigue compared to the HP group.

Study limitations

A limitation of this study is related to the low number of FSHD1 patients and HP included. The reasons may be as follows: i) the pool of patients with FSHD1 is rather low and/or geographically spread, ii) it is unlikely to include enough patients with FSHD1 that have the identical muscle weakness as well as possible matching response to the training program. Nevertheless, all the participants completed the NMES training sessions scheduled. Second, the heterogeneity of the adaptations to the NMES training program may have been too important to highlight specific adaptations within each group. Also, no FSHD1 control group (i.e., FSHD 1 patients not receiving NMES) was included in order to assess the possible changes of measured variables due to the progression of the disease during the 8-week period. Then, although the reliability of strength measurements is often questionable in fragile populations, the measurements seemed to be sufficiently accurate since interclass correlation coefficient for the ankle dorsiflexion MVC ranged from 0.96 (right leg) to 0.98 (left leg) and

from 0.87 (right leg) to 0.93 (left leg) for the associated TA EMG RMS values. Notwithstanding these limitations, the present results may be useful to assist clinicians to plan in the design of rehabilitation programs with the use of NMES in FSHD1 patients. For example, in light of the present results and based on the literature, we proposed that future clinical studies should design NMES training programs including between three to five training sessions per week (for a muscle group) with frequencies ranging above 50 Hz with a pulse duration ranging from 100µs to 500µs for a minimum duration of 20 to 30 minutes (duty cycle ~50%). Although the exact training duration period has yet to be determined, a minimum of three months seemed required to expect positive adaptations.

## CONCLUSION

In summary, the present results show that an 8-week bilateral NMES training (20 minutes per session, 3 sessions per week) of the tibialis anterior muscle did not improve muscle strength, endurance and motor function in patients with FSHD1. Whether this non-responsiveness is due to the impaired neuromuscular function of the ankle dorsiflexor muscles and/or to the duration of the NMES protocol or to the stimulation intensity level reached during the NMES sessions still remain to be shown. As suggested by Colson et al.[17], it is likely that the efficacy of the NMES training would depend on rapidity of starting NMES training as soon as the FSHD1 diagnosis is made to maximize the training effects.

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## FIGURES LEGENDS

**Figure 1A** Box-plots of the dorsiflexion Maximal Voluntary Contraction (N) for the FSHD1 patients and the HP groups for the right and left legs, before (dark fill-in) and after (white fill-in) the NMES training. Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Significant group differences $p<0.001$ (***).

**Figure 1B** Box-plots of the RMS amplitude of the Tibialis Anterior during the dorsiflexion Maximal Voluntary Contraction for the FSHD1 patients and the HP groups for the right and left legs, before (dark fill-in) and after (white fill-in) the NMES training. Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Significant group differences $p<0.05$ (*) and $p<0.001$ (***).

**Figure 2**. Box-plot of the percentage of force production loss (A, left panel) and of the RMS of the tibialis anterior (TA) (B, right panel) during the 2-minute sustained ankle dorsiflexion endurance exercise, for the right and left legs, before (dark fill-in) and after (white fill-in) the 8-week training for patients with facioscapulohumeral muscular dystrophy (FSHD1) and healthy participants (HP). Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Columns represent group mean values and error bars the standard error of the group mean. Significant group differences: $p<0.05$ (*), $p<0.01$ (**).

**Figure 3** Box-plot of the manual muscle testing (MMT) of the dorsiflexion for both for legs obtained before (dark fill-in) and after (white fill-in) the 8-week training period for facioscapulohumeral muscular dystrophy (FSHD1). Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Dashed lines display individual data.

**Figure 4** Mean and standard error (mean ± SE) of the stimulation intensity (mA) for the FSHD1 (grey line) and the HP (black line) for the right (plain lines) and left (dashed lines) throughout the 24 sessions of the 8-week NMES training.

**Title:** Short-term neuromuscular electrical stimulation training of the tibialis anterior did not improve strength and motor function in facioscapulohumeral muscular dystrophy patients


## ABSTRACT

Objective: To investigate the effects on motor function, muscle strength and endurance of short term neuromuscular electrical stimulation (NMES) training of the *tibialis anterior* (TA) muscles in patients with facioscapulohumeral muscular dystrophy type 1 (FSHD1) in comparison with healthy controls.

Design: This prospective study included ten patients with FSHD1 and ten healthy participants (HP). Maximal voluntary isometric contraction (MVC) of ankle dorsiflexion (DF) and a 2-minute sustained DF MVC with surface electromyography recordings (sEMG) of the TA and the soleus muscles were measured and motor function clinical tests were performed before and after the training period.

Results: No significant short term training effect was found in any of the investigated variables for either group, although a tendency towards an increase was noted for the manual muscle testing of the FSHD1. Patients with FSHD1 showed lower MVC force and lower maximal TA sEMG amplitude than HP. During the 2-minute sustained MVC, the percentage of force loss was lower for the FSHD1 patients, suggesting that they were experiencing a lower amount of muscle fatigue compared to the HP group.

Conclusion: The present NMES protocol was not strenuous enough and/or the parameters of stimulation were not adequate to improve dorsiflexion strength, muscle endurance and motor function in FSHD1 patients and HP.

**KEY WORDS**: Isometric strength; Muscle endurance; Electromyography; Neuromuscular disorder

## INTRODUCTION

With a European prevalence of 4/100,000, the facioscapulohumeral muscular dystrophy (FSHD) is the most common inherited muscular dystrophy disease. The FSHD is genetically heterogeneous and two types of FSHD (*i.e.,* FSHD1, 95% of patients and FSHD2, 5% of patients) have been identified.[1] Independently of the type of FSHD (*i.e.,* 1 or 2), the disease is characterized by a progressive asymmetric muscle weakness and atrophy usually spreading form facial to shoulder girdle, arms, abdominal and lower limb muscles.[2] In addition to muscle weakness, fatigue and pain are the two other most frequently reported symptoms. In particular, severe fatigue, a major burden in daily life activities, is reported by 61% of patients with FSHD [3] conducting to a sedentary lifestyle through a reduced level of physical activity.[4] The reduced level of muscle strength has been identified as a key factor in explaining low level of physical activity and high experienced fatigue.[5] In patients with FSHD1, *tibialis anterior* muscles can be affected in earlier stages of the disease than other lower limb muscles [6,7] and this decline in *tibialis anterior* function is frequently considered as the first disabling symptom.[8] Since the *tibialis anterior* has a strong functional role in gait and balance, both its weakness and fatigue may lead to a loss of mobility and increase the risk of falling.[4] Since no therapeutic treatments are yet available for FSHD,[2] it is of interest to propose alternative procedures to moderate the progressive loss of strength, endurance and muscle function.

Aerobic exercises have been proposed to improve muscle function in patients with FSHD, but some studies failed to show improvements on strength of such training, even though no deleterious effects were reported.[9,10] Neuromuscular electrical stimulation (NMES) is another type of exercise broadly used in rehabilitation settings.[11] When NMES training was performed on patients suffering from disabling forms of muscular dystrophy, such as Duchenne and Becker dystrophies, tolerance and efficacy were shown to maintain or even improve muscle strength.[12–15] Comparable results in the *tibialis anterior* and the quadriceps muscles were

reported in a group of mixed patients with neuromuscular disorders including patients with FSHD.[16] More recently, NMES training, performed on shoulder girdle and knee extensor muscles, was found to be safe and effective in improving strength and muscle function in patients with FSHD1.[17] The two studies that have investigated the NMES training programs in FSHD[16,17] involved long training periods of 14 and 5 months respectively. Although beneficial effects of short term (less than 8 weeks) NMES training programs on muscle strength and/or endurance in healthy participants[18,19] or patients with muscular dystrophy[12] were found, such programs have not been implemented in patients with FSHD. Therefore, the objective of this study was to investigate the effect of a bilateral 8-week NMES training on the *tibialis anterior* muscle in adults with FSHD1. It was hypothesized to observe muscle strength and endurance gains in dorsiflexion as well as improved motor function in patients with FSHD1.

## METHODS

### Participants

Ten adults with FSHD1 (mean ± standard deviation (SD): 5 females and 5 males; age 62.3 ± 10.2 year; height: 168.5 ± 12.8 cm; body mass: 73.7 ± 15.2 kg) and 10 healthy participants (HP) age matched (7 females and 3 males; age 56 ± 4.8 year; height: 171.5 ± 9.01 cm; body mass: 74.8 ± 12.4 kg) volunteered to take part in the study and written informed consent was obtained from all participants. The study was carried out according to the Declaration of Helsinki and approved by the local Institutional Human Ethics Committee. The trial was declared.

Adults patients diagnosed with FSHD1 were recruited from the outpatient record of the physical medicine and rehabilitation department at the hospital and were included into the

78 study according to the following criteria: number of 4q35 D4Z4 <11 repeats (mean of the
79 group 6.89 ± 1.37 units), no mutation on *SMCHD1* gene ; muscle weakness of ankle
80 dorsiflexion from 2 to 4 at least on one leg, assessed by manual muscle testing (MMT).[20]
81 Exclusion criteria comprised previous NMES training of the lower-limb; history of cancer,
82 joints pathologies, or collagenopathies, parturient, or breast-feeding woman or simultaneous
83 participation to another research study.
84
85 **Neuromuscular electrical stimulation training**
86 Bilateral neuromuscular electrical stimulation (NMES) training sessions of the *tibialis*
87 *anterior* muscles were performed with a Compex (Rehab 400, Cefar-Compex, DJO France
88 SAS, Mouguerre, France) portable battery-powered stimulator. Participants either exercised at
89 home or were trained by one of the experimenters or a physiotherapist. All healthy
90 participants as well as four patients with FSHD1 carried out their training sessions at home. In
91 the case participants trained at home, a weekly appointment was set-up with one of the
92 experimenters to provide feedback and to control the quality of the training. During these
93 training sessions participants were seated (hips, knees and ankles angles at 90°) with their feet
94 fixed. During the training sessions, the participants were instructed to place comfortably their
95 feet under a heavy-weighted object so that the feet would be firmly stuck and would not move
96 during the contractions. The participants were simultaneously stimulated bilaterally with self-
97 adhesive electrodes (2 mm thick) made of elastomer (5 cm x 5 cm) that were positioned as
98 follows: the positive electrode was placed on the superior part of the muscle, whereas the
99 negative electrode was placed on the medial part of the muscle, over the muscle bulk.
100 The NMES training program lasted for 8 weeks, with 3 sessions a week. Each session was
101 composed of a 2-minute warm-up, followed by the 20-minute working out session, and
102 finishing with 3 minutes of relaxation. The NMES program consisted in isometric

contractions of 9s (rise time: 1.5s; steady tetanic stimulation time: 6s; fall time: 1.5s) followed by a pause lasting 7 seconds (duty cycle: 56.25%) at 35 Hz and with a 200µs pulse-width. These stimulation parameters were chosen accordingly to previous successful NMES using low-frequency protocols in patients with neuromuscular disorders to increase muscle strength. [12–17] Participants were encouraged to increase stimulation intensity progressively every 5 minutes throughout each session up to individual tolerance threshold (i.e., discomfort/pain) since strength gains would be dependent on the stimulation intensity.[21,22] As individual tolerance threshold varied among participants, they were instructed to increase progressively stimulation intensity during the warm-up period to ensure a visible muscle contraction. However, since the feet were secured, no joint movement was induced. Moreover, during each of the training sessions, the participants or the physiotherapist, according to the training modality (i.e., supervised or at home) had to fill-out a questionnaire consisting in reporting the following: date and time of the training session; the mean intensity of the neuromuscular electrical stimulation delivered; self-evaluation of their perceived fatigue after the training session; the discomfort related to the NMES delivered during training sessions. Visual analogue scales (VAS) were used to score perceived fatigue and discomfort. A score of 0 mm indicated no fatigue or no discomfort and 100 mm indicated unbearable fatigue or maximum discomfort.

**Study design**

To disclose the effect of the 8-week NMES training, at pre and post training, the participants had first a blood sample collection, followed by a clinical examination and neuromuscular tests. Following this, they answered a questionnaire during a 30 min period of rest and then performed a 6-min walk test (6MWT).

*Blood samples collection*

To establish tolerance to NMES training, Plasma Creatine Kinase (CK) was measured after the fourth week (W4), and once randomly during the training in addition to before and after the 8-week training period (W8). Blood samples were collected and analyzed at the hospital. The first and last CK measurements were determined at rest, whereas the 4-week and the random test were performed within two hours following the NMES training. Plasma CK activity was determined spectrophotometrically by an automatic analyzer using a test kit (Roche/Hitachi Automated Clinical Chemistry Analyzer, Modular P-800, Roche Diagnostics, Meylan, France). The CK activity was considered as a biological marker of training-induced damage for each participant.

*Clinical examination*

Muscle function and strength of the TA were assessed manually by a physiotherapist, by manual muscle testing - MMT.[20] Depending on the amplitude of the ankle dorsiflexion, without extension of the hallux, scores were ranked from 0 where the muscle is no longer capable of force production to 5 representing the absence of muscle impairment.

The Motor Function Measurement (MFM) assessed the functional capacity of daily life activities: standing still, weight transfers, sitting, proximal and distal motor ability of muscles, walking, standing up, raising up arms, stepping up stairs, brush hairs *etc*. After evaluation, the total score was presented as a percentage, with healthy participants reaching 100%.[23] The physiotherapist performing the clinical examination was experienced to assess patients suffering from neuromuscular disorders and was not blinded to the evaluation.

*Neuromuscular tests*

Maximal voluntary contractions (MVC) of the dorsiflexor muscles were carried out unilaterally in a custom made device [24] consisting of a fixed footplate, where the foot was firmly strapped to avoid any movement and ensure the quality of the isometric force measurement. A strain-gauged transducer (model OMF06M, linear range 0-15 kN, precision ± 0.5 %, sensitivity 10 mV/kN; OMICRO'N, Gambais, France) was placed on the footplate to measure force production. During all contractions, the participants were seated on a chair, with their knee slightly flexed according to the comfort of the participant. The foot was firmly tightened with belts over the footplate with an ankle angle of 90°. The participants were not constrained and were allowed to seat as comfortably as they could, however, during MVCs, they were not allowed to hold the seat and were asked to remain as steady as they could.

Bipolar surface electromyography (sEMG) electrodes (10 mm diameter, 20 mm inter-electrode distance) recorded the electrical activity of the tibialis anterior (TA) and the soleus (SOL) muscles. The reference electrode was placed on the bony part of the contralateral patella. Skin was cleaned and abraded prior to the placement of electrodes, and low resistance impedance between electrodes (<5 kΩ) was obtained. A Biopac MP 150 system (Biopac systems, Inc., Holliston, MA, USA) was used to record sEMG data at a sampling rate of 2000 Hz. Electromyographic signals were amplified with a bandwidth frequency ranging from 1 Hz to 500 Hz (common mode rejection ratio = 11 dB; impedance input = 1000 MV; gain = 1000).

The tests were performed on both legs, one at a time, in a random order with at least 10 minutes of rest period between each leg. Two MVCs of dorsiflexion were performed on each leg to determine the maximal strength production and the concomitant sEMG signals of both the TA and the SOL muscles. A 60-second rest was allowed between each contraction. Then, a fatiguing task consisting of an isometric 2-minute MVC [25] of dorsiflexion was performed with recordings of the sEMG of TA and SOL muscles. No visual feedback was provided to

the participants and they were asked to perform an all-out effort while they received strong verbal encouragement.

*Questionnaire and 6-min walk test*

Quality of life of the participants was evaluated with the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire.[26] A 6-min walk test (6MWT) was used to assess the greatest distance participants could walk in 6 minutes on a 20-meter shuttle.

**Data analysis**

The MVC was considered as the mean value over a 500-ms period around the peak force. The best of the two trials was analyzed. During the fatiguing task, the percentage of MVC loss was calculated as the difference of a 1-second window width at the start and a 1-second window width at the end of the 2-minute MVCs. All sEMG data were analyzed over the same window width as the force data where the root mean square (RMS) of the TA and the SOL (TA RMS and SOL RMS) was quantified and the loss in TA RMS was computed. RMS was calculated with commercially available software (AcqKnowledge 4.1, Biopac Systems, Inc., Holliston, MA, USA), while the rest of the outcome measures were analyzed with Matlab R2010b (The MathWorks, Inc., Natick, MA, United-States).

**Statistical analysis**

Statistical processing was performed using Statistica® software for Microsoft Windows (StatSoft, version 8.0, Tulsa, OK, USA). The Shapiro-Wilk test was used to test whether outcome measures were normally distributed, and depending on the results the appropriate statistical test was performed. When data were normally distributed, an unpaired Student t-test was performed to compare FSHD1 and HP groups and a paired Student t-test was used to disclose training-induced changes within group (FSHD1 and HP). When data did not follow a normal distribution, equivalent non-parametric tests, the Mann-Whitney *U* test and the Wilcoxon signed ranks test were performed. A two-way ANOVA (leg × time) with repeated measures on time was performed on the intensity values recorded during each training session, while the Friedman ANOVA was applied for the discomfort and fatigue VAS values as they did not follow a normal distribution. In all statistical analysis the significance level was set at $p<0.05$. Unless specified, normal distributed data are expressed as means ± SD (standard deviation of the mean), in the entire manuscript and in the tables and figures, while

non-normally distributed data are expressed as median ± IQR (inter quartile range) in tables and box-plots are used in figures.

## RESULTS

### FSHD1 patients and healthy participants before the training period

The plasma CK concentration was higher in FSHD1 patients before the training period (t=4.38; $p<0.001$; Table 1). The MMT (Right: U=5.0; $p<0.001$; Left: U=0.0; $p<0.001$;) and MFM scores of the FSHD1 patients were significantly impaired compared to the HP before the training period (U=0.0; $p<0.001$; Table 1). Similarly, the distance covered during the 6MWT by the FSHD1 patients was shorter compared to the HP (t=-2.63; $p=0.02$; Table 1). Lastly, quality of life assessed by means of SF-36 questionnaire (Table 2) revealed lower values of FSHD1 patients compared to the HP for the following subscores: physical functioning (U=6.5; $p<0.001$), social functioning (U=18.0; $p<0.05$), vitality (U=14.5; $p<0.05$), general health (U=5.0; $p<0.001$) and the standardized physical component (U=7.0; $p<0.01$).

*Neuromuscular tests and fatiguing task*

As illustrated in the Figure 1A, the peak force during ankle dorsiflexion MVC was significantly lower in FSHD patients than in HP prior to the training period for both legs (Right, Pre: U=88.0; $p<0.001$; Left, Pre: U=102.0; $p<0.001$). The associated amplitude of the TA RMS during dorsiflexion MVC (Figure 1B) was lower in the FSHD1 patients compared to the HP before (Right: U=95.0; $p<0.001$; Left: U=90.0; $p=0.013$) the training period. In addition, the amplitude of the SOL RMS during dorsiflexion MVC was found lower in the FSHD1 patients before on the right leg (U=85.0; $p=0.007$), but not on the left leg ($p=0.282$). Although not significantly different for the left leg ($p=0.095$), the group of patients with FSHD1 exhibited a lower force reduction during the 2-minute MVC than the HP group before

the training period on the right leg (Right: U=10.0; $p$=0.003; Figure 2A). No difference in percentage of TA RMS and SOL RMS reduction between groups was found before the training period for either leg ($p$>0.05).

**Effects of NMES training in FSHD1 patients and healthy participants**

Individual patient/healthy participant's compliance to the training program was maximal (i.e., 100% of the scheduled training sessions attended). Whatever the group considered, plasma CK did not change significantly during the NMES training period ($p$>0.05). The NMES training did not modify the SF-36 questionnaire subscores and the values of the FSHD1 patients remained lower than those of the HP (Table 2). Also, no significant changes of the MFM and 6MWT assessments were observed after the training period ($p$>0.05) and the values of the FSHD1 patients remained lower than those of the HP (Table 1). Although no significant differences were found, the MMT values of the FSHD1 patients tended to slightly increase after the training period ($p$=0.067; Figure 3) for both the right and left legs. Also, when considering exclusively legs (i.e., fourteen legs) matching the inclusion criterion of having a MMT score of ankle dorsiflexion comprised between 2 to 4, a significant training effect was observed ($p$=0.027; data not illustrated).

*Neuromuscular tests and fatiguing task*

No significant training effect was found in dorsiflexion strength ($p$>0.05; Figure 1A) and in the associated RMS amplitude of the TA ($p$>0.05; Figure 1B) and the SOL muscles in either group for both sides. All these variables of the FSHD1 patients remained lower than those of the HP (Figures 1 and 2).

The force reduction during the 2-minute MVC did not changed after the training period for both legs in the FSHD1 patients and HP ($p$>0.05; Figure 2A). Although no significant

difference was found for the left leg, the TA RMS reduction of the right leg during the 2-minute MVC was significantly greater after the training period for the FSHD1 patients (t=3.33; $p>0.05$; Figure 2B). No significant change was noted for the HP. Also, no change of the SOL RMS reduction was found after the training period for either leg or group.

*Characteristics of the NMES training program*

As illustrated in the Figure 4, the stimulation intensity of the NMES training was significantly increased for the FSHD1 groups on both legs (F=1.89; $p<0.05$) as well as for the HP (F=3.26; $p<0.001$). The self-reported evaluation of the discomfort level throughout the training reduced on the right leg only in the group of patients with FSHD1 ($\chi^2$=36.1; $p$=0.041; Left leg: $\chi^2$=28.2; $p$=0.208), whereas no change was observed for the group of healthy participants ($p>0.05$). Likewise, the self-reported fatigue level reduced significantly in the group of patients with FSHD1 along the training only in the left leg (Left leg: $\chi^2$=40.3; $p$=0.014; Right leg: $\chi^2$=34.3; $p$=0.061). No change was observed for either leg in the HP group ($p>0.05$).

## DISCUSSION

The purpose of this study was to investigate whether a short term bilateral NMES training on the *tibialis anterior* muscles in adults with FSHD1 would be well tolerated and would improve muscle strength, endurance and motor function. All participants completed the 8-week NMES training program and no side effects were reported during or after the training period. Unfortunately, this program did not improve ankle dorsiflexion maximal muscle strength, nor muscle endurance or motor function in patients with FSHD1, although a tendency towards an increase was observed for the MMT scores. Also, no significant improvements were noted for the healthy participants.

All the participants (*i.e.,* FSHD1 patients and HP) completed the NMES training program and according to the CK measurements, no rhabdomyolysis was induced by the NMES protocol. Also, discomfort and fatigue VAS values reported throughout the protocol remained clinically low (mean VAS<2) and did not significantly increase during the 8-week period. These results agree with previous studies investigating the effects of NMES training programs in neuromuscular diseases[17] and confirm that NMES exercise is well tolerated by FSHD1 patients and HP.

Although well tolerated, this study failed to show a positive significant effect of NMES on muscle strength, muscle endurance and motor function of the ankle dorsiflexor muscles in FSHD1 patients, as well as in the HP. These observations are somehow surprising considering that benefits of NMES training programs on muscle strength are widely reported in literature for similar, or even shorter training periods in healthy participants [18,19]. In addition, the use of NMES was shown to be effective in patients with muscular dystrophies [12–15] and in patients with FSHD1.[16,17]

Although, the characteristics of stimulation parameters used here (35 Hz of frequency and 200-µs pulse duration) may be questioned, these NMES parameters were chosen since they were successfully used in previous rehabilitation settings in patients with muscular dystrophies.[13,17] However, FSHD1 patients can have fat infiltration in TA muscles [6,27] and strong alteration of the sarcomeric contractile properties, preferentially of type II fibers,[28,1] reducing the overall capacity of the muscle to contract. Nevertheless, this reason cannot account for the absence of improvements in the HP. Considering that frequencies above 50 Hz are suggested to maximize the training effect of NMES on muscle strength in healthy participants,[22] it may be suggested that these frequencies should be considered in future NMES studies in FSHD1 patients.

The lack of significant improvements could also be attributable to the frequency of the sessions and/or the duration of the training. Only three sessions per week for eight weeks were performed, whereas Colson et al.[17] trained their FSHD1 patients five days per week over a 5-month training period. Similarly, Milner-Brown and Miller[16] obtained significant improvement in strength after a 2-hour session performed 5 days per week during 14 months. Therefore, a higher volume training period (greater number of sessions or duration) might be required to obtained significant strength improvements in FSHD1 patients. Finally, as previously suggested, the stimulation intensity was constantly increased throughout the training period to ensure strength adaptations.[22] However, this stimulation intensity increment might have been too moderate to improve muscle strength. Therefore, it seems that the main reason for the absence of strength increase in FSHD1 patients has to be related to the frequency and/volume of the NMES sessions. Moreover, in the FSHD1 patients, the impaired muscle function of the TA at the beginning of the study can be suggested as a possible reason candidate for the training to be ineffective. Since no training effect was seen in the HP group either, this cannot be stated with certitude. Finally, the *soleus* muscle activity of the right leg during the dorsiflexion was found to be of lower magnitude compared to the left leg for the FSHD1 patients before the training. This observation confirms that important imbalance exits between limbs (i.e., asymmetric muscle weakness) and that particular neuromuscular adjustments/compensations could occur with the disease in order to maintain functional movements. These neuromuscular imbalances and their influence on functional daily tasks such as balance/walking should be further investigated in FSHD patients.

Interestingly and although it did not change with the training period, the MVC loss was much lower in the FSHD1 patients than in the HP during the 2-minute fatiguing task. This may indicate that patients with FSHD1 experienced a lower amount of muscle fatigue compared to the HP,[25] before and after the training, likely for several reasons. First, as the amplitude of the

TA EMG RMS reduced similarly, this suggests that the neural drive to the muscles would have become suboptimal with fatigue for both groups in the same fashion during the fatiguing exercise.[29] Second, patients with FSHD1 have strong alteration of the sarcomeric contractile properties of type II fibers,[1,28] which could lead to muscles more resistant to fatigue. Third, weaker participants are shown to be less fatigable than stronger ones,[30] as the intramuscular pressure is lower the negative feedback from afferent groups III and IV is therefore diminished.[30] Even though, the group of patients with FSHD1 showed a greater TA EMG RMS loss after the training in comparison to the loss before the training, this decrease was similar in both groups. Since the patients group showed lower force losses, it can be suggested that at the task truncation, the group of patients with FSHD were experiencing a lower amount of muscle fatigue compared to the HP group.

Study limitations

A limitation of this study is related to the low number of FSHD1 patients and HP included. The reasons may be as follows: i) the pool of patients with FSHD1 is rather low and/or geographically spread, ii) it is unlikely to include enough patients with FSHD1 that have the identical muscle weakness as well as possible matching response to the training program. Nevertheless, all the participants completed the NMES training sessions scheduled. Second, the heterogeneity of the adaptations to the NMES training program may have been too important to highlight specific adaptations within each group. Also, no FSHD1 control group (i.e., FSHD 1 patients not receiving NMES) was included in order to assess the possible changes of measured variables due to the progression of the disease during the 8-week period. Then, although the reliability of strength measurements is often questionable in fragile populations, the measurements seemed to be sufficiently accurate since interclass correlation coefficient for the ankle dorsiflexion MVC ranged from 0.96 (right leg) to 0.98 (left leg) and

from 0.87 (right leg) to 0.93 (left leg) for the associated TA EMG RMS values. Notwithstanding these limitations, the present results may be useful to assist clinicians to plan in the design of rehabilitation programs with the use of NMES in FSHD1 patients. For example, in light of the present results and based on the literature, we proposed that future clinical studies should design NMES training programs including between three to five training sessions per week (for a muscle group) with frequencies ranging from above 50 Hz with a pulse duration ranging from 100µs to 500µs for a minimum duration of 20 to 30 minutes (duty cycle ~50%). Although the exact training duration period has yet to be determined, a minimum of three months seemed required to expect positive adaptations.

## CONCLUSION

In summary, the present results show that an 8-week bilateral NMES training (20 minutes per session, 3 sessions per week) of the tibialis anterior muscle did not improve muscle strength, endurance and motor function in patients with FSHD1. Whether this non-responsiveness is due to the impaired neuromuscular function of the ankle dorsiflexor muscles and/or to the duration of the NMES protocol or to the stimulation intensity level reached during the NMES sessions still remain to be shown. As suggested by Colson et al.[17], it is likely that the efficacy of the NMES training would depend on rapidity of starting NMES training as soon as the FSHD1 diagnosis is made to maximize the training effects.

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## FIGURES LEGENDS

**Figure 1A** Box-plots of the dorsiflexion Maximal Voluntary Contraction (N) for the FSHD1 patients and the HP groups for the right and left legs, before (dark fill-in) and after (white fill-in) the NMES training. Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Significant group differences $p<0.001$ (***).

**Figure 1B** Box-plots of the RMS amplitude of the Tibialis Anterior during the dorsiflexion Maximal Voluntary Contraction for the FSHD1 patients and the HP groups for the right and left legs, before (dark fill-in) and after (white fill-in) the NMES training. Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Significant group differences $p<0.05$ (*) and $p<0.001$ (***).

**Figure 2**. Box-plot of the percentage of force production loss (A, left panel) and of the RMS of the tibialis anterior (TA) (B, right panel) during the 2-minute sustained ankle dorsiflexion endurance exercise, for the right and left legs, before (dark fill-in) and after (white fill-in) the 8-week training for patients with facioscapulohumeral muscular dystrophy (FSHD1) and healthy participants (HP). Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Columns represent group mean values and error bars the standard error of the group mean. Significant group differences: $p<0.05$ (*), $p<0.01$ (**).

**Figure 3** Box-plot of the manual muscle testing (MMT) of the dorsiflexion for both for legs obtained before (dark fill-in) and after (white fill-in) the 8-week training period for facioscapulohumeral muscular dystrophy (FSHD1). Boxes represent group median and interquartile range values and whiskers are the highest and lowest values. Dashed lines display individual data.

**Figure 4** Mean and standard error (mean ± SE) of the stimulation intensity (mA) for the FSHD1 (grey line) and the HP (black line) for the right (plain lines) and left (dashed lines) throughout the 24 sessions of the 8-week NMES training.

**Table 1**. Mean and standard deviation (mean ± SD) of the plasma Creatine Kinase (CK) values obtained before training (Pre), after the fourth week (Mid), after the 8-week training period (Post) and during the random measurement made during the training period after the training session (Random), as well as the motor function measurement (MFM) and the 6-min walk test performance obtained before (Pre) and after (Post) the 8-week training period for facioscapulohumeral muscular dystrophy (FSHD1) and healthy participants (HP).

| CK (U/L) | **FSHD1** | **HP** |
|---|---|---|
| CK (U/L) | | |
| *Pre* | 213.1 ± 46.7 | 118.6 ± 38.3*** |
| *Mid* | 185.5 ± 52.7 | 131.4 ± 49.7 |
| *Post* | 208.3 ± 48.5 | 124.8 ± 40.6*** |
| *Random* | 205.8 ± 32.4 | 119.9 ± 37.4*** |
| MFM | | |
| *Pre* | 68.86 ± 19.35 | 100.0 ± 0.0*** |
| *Post* | 66.97 ± 17.42 | 100.0 ± 0.0*** |
| 6-min walk test (m) | | |
| *Pre* | 309.67 ± 132.14 | 462.22 ± 113.66* |
| *Post* | 311.11 ± 126.88 | 475.25 ± 131.07* |

Significantly different from FSHD1: *** $p<0.001$; ** $p<0.01$; * $p<0.05$

**Table 2**. Medical Outcomes Study Short-Form 36 (SF-36) scores obtained before (Pre) and after (Post) the 8-week training period for patients with facioscapulohumeral muscular dystrophy (FSHD1) and healthy participants (HP).

| | **FSHD1** | | **HP** | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| *SF-36 subscores* | | | | |
| Physical Functioning | 43.0 ± 30.1 | 35.0 ± 22.2 | 92.5 ± 12.8*** | 96.5 ± 6.7 |
| Physical role | 70.0 ± 32.9 | 71.9 ± 41.1 | 92.5 ± 23.8 | 90.0 ± 21.1 |
| Bodily pain | 57.5 ± 23.6 | 52.6 ± 24.9 | 80.0 ± 23.6 | 80.9 ± 23.1 |
| Mental Health | 75.6 ± 14.9 | 73.0 ± 16.1 | 84.0 ± 13.7 | 81.6 ± 20.0 |
| Emotional role | 96.3 ± 11.1 | 70.8 ± 45.2 | 100.0 ± 0.0 | 100.0 ± 0.0 |
| Social Functioning | 75.0 ± 21.5 | 75.0 ± 22.2 | 97.5 ± 7.9* | 93.8 ± 15.9 |
| Vitality (Energy/Fatigue) | 48.9 ± 20.4 | 47.3 ± 17.8 | 74.0 ± 16.6* | 72.5 ± 22.9 |
| General Health | 59.9 ± 14.9 | 50.4 ± 17.6 | 87.4 ± 11.9*** | 87.4 ± 15.6 |
| Health Change | 50.0 ± 28.9 | 43.8 ± 17.7 | 57.5 ± 23.7 | 57.5 ± 16.9 |
| Standardized physical component | 34.9 ± 11.5 | 34.8 ± 7.9 | 53.1 ± 6.2** | 53.4 ± 5.3 |
| Standardized mental component | 55.8 ± 3.7 | 52.0 ± 10.4 | 56.6 ± 5.3 | 54.9 ± 9.3 |

Significantly different from FSHD1: *** $p<0.001$; ** $p<0.01$; * $p<0.05$

Figure 1A

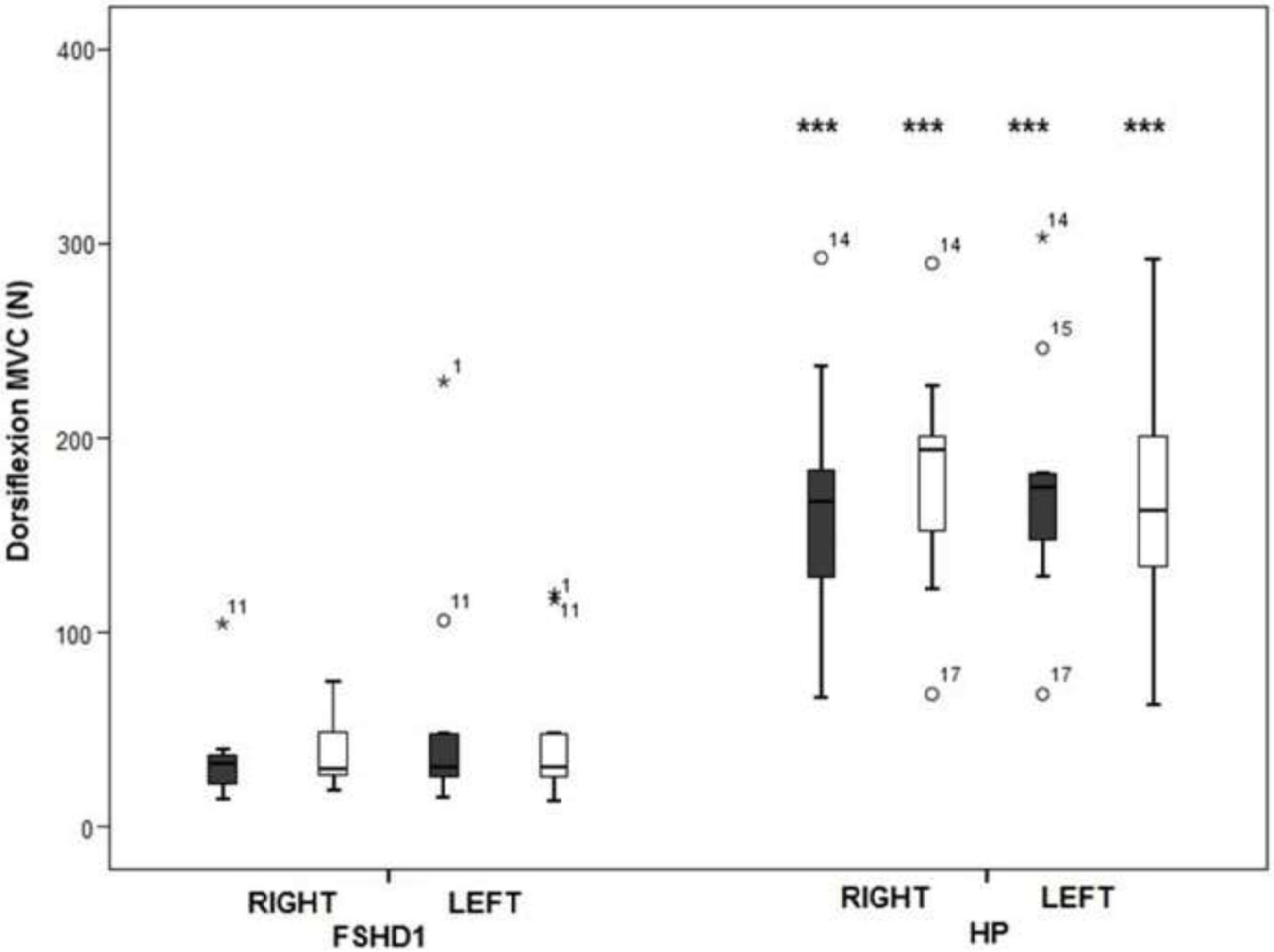

Dorsiflexion MVC (N)
400
300
200
100
0
***
***
***
***
14
14
14
15
1
11
11
1
11
17
17
RIGHT
LEFT
FSHD1
RIGHT
LEFT
HP

Figure 1B

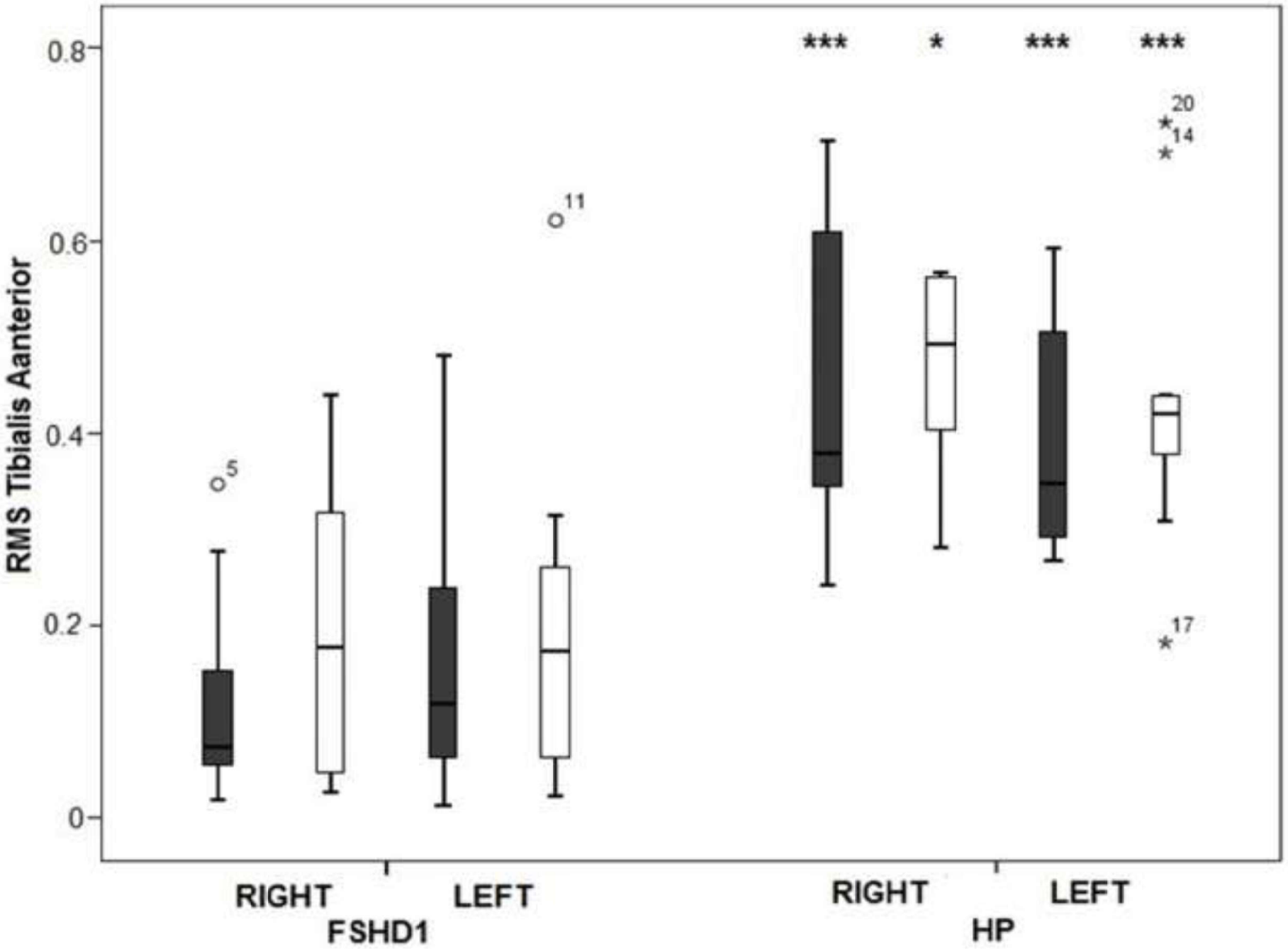

RMS Tibialis Aanterior
0.8
0.6
0.4
0.2
0
***
*
***
***
20
14
17
11
5
RIGHT
LEFT
FSHD1
RIGHT
LEFT
HP

Figure 2A

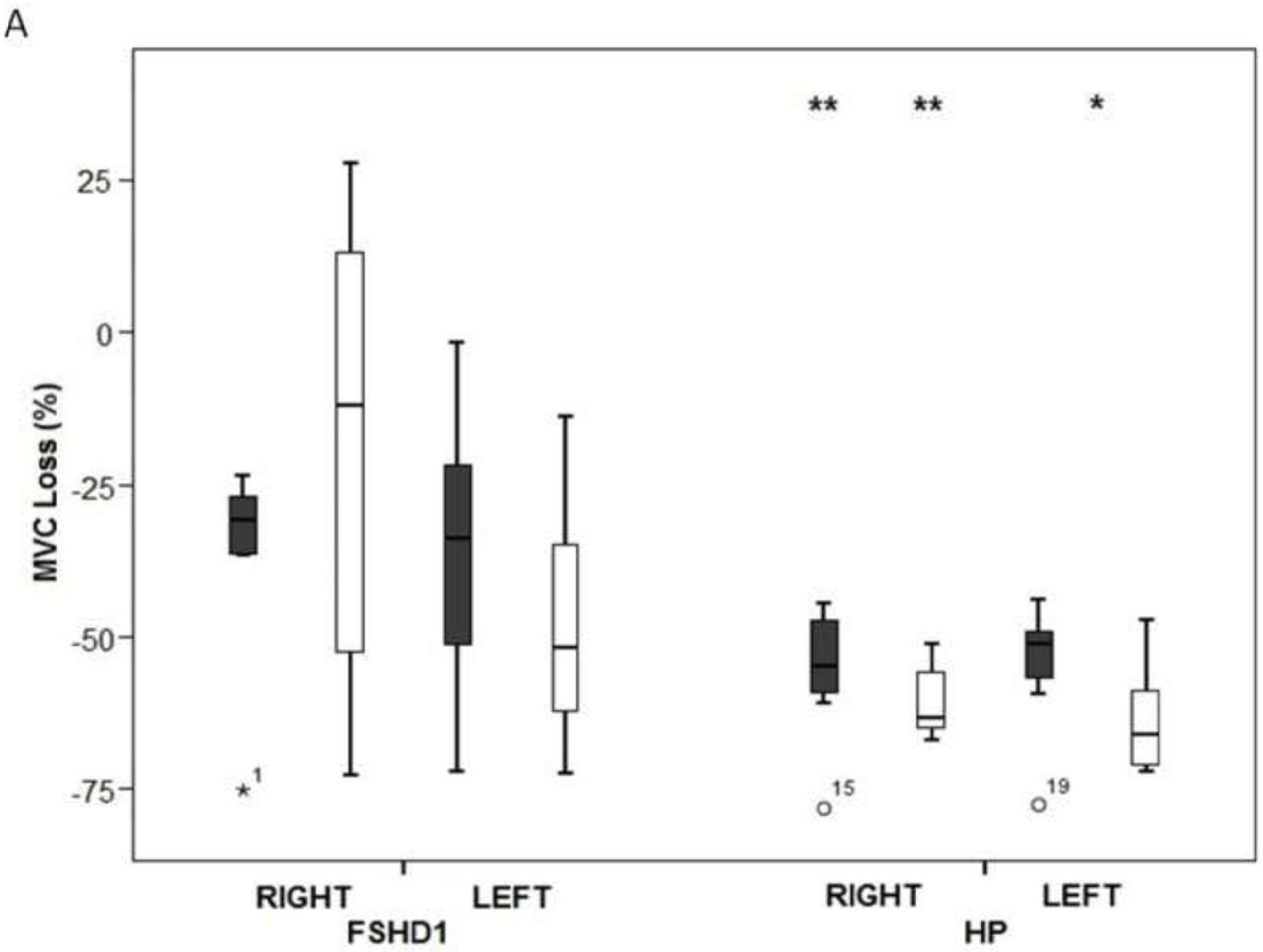


Figure 2B

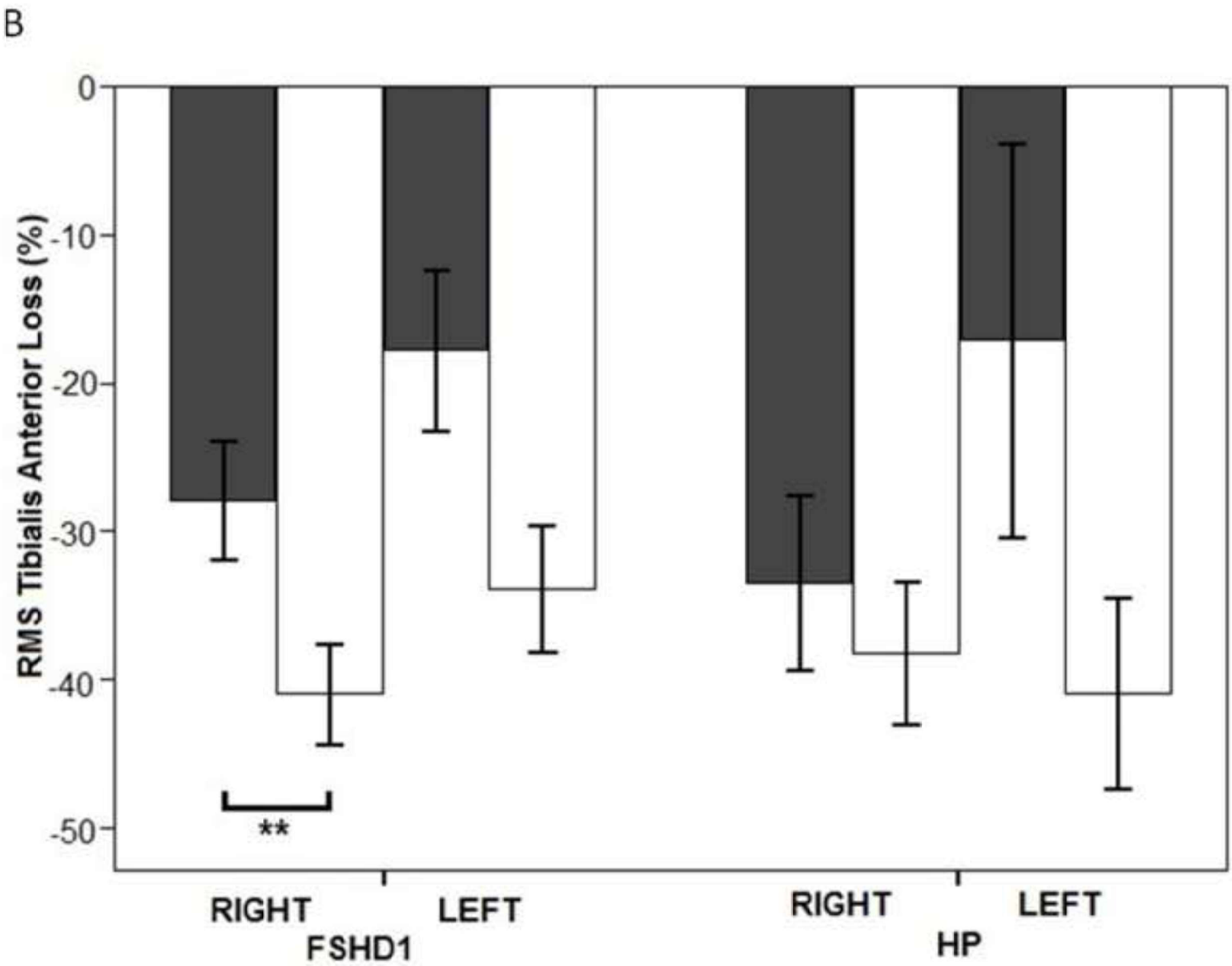

B
0
-10
-20
-30
-40
-50
RMS Tibialis Anterior Loss (%)
**
RIGHT
LEFT
FSHD1
RIGHT
LEFT
HP

Figure 3

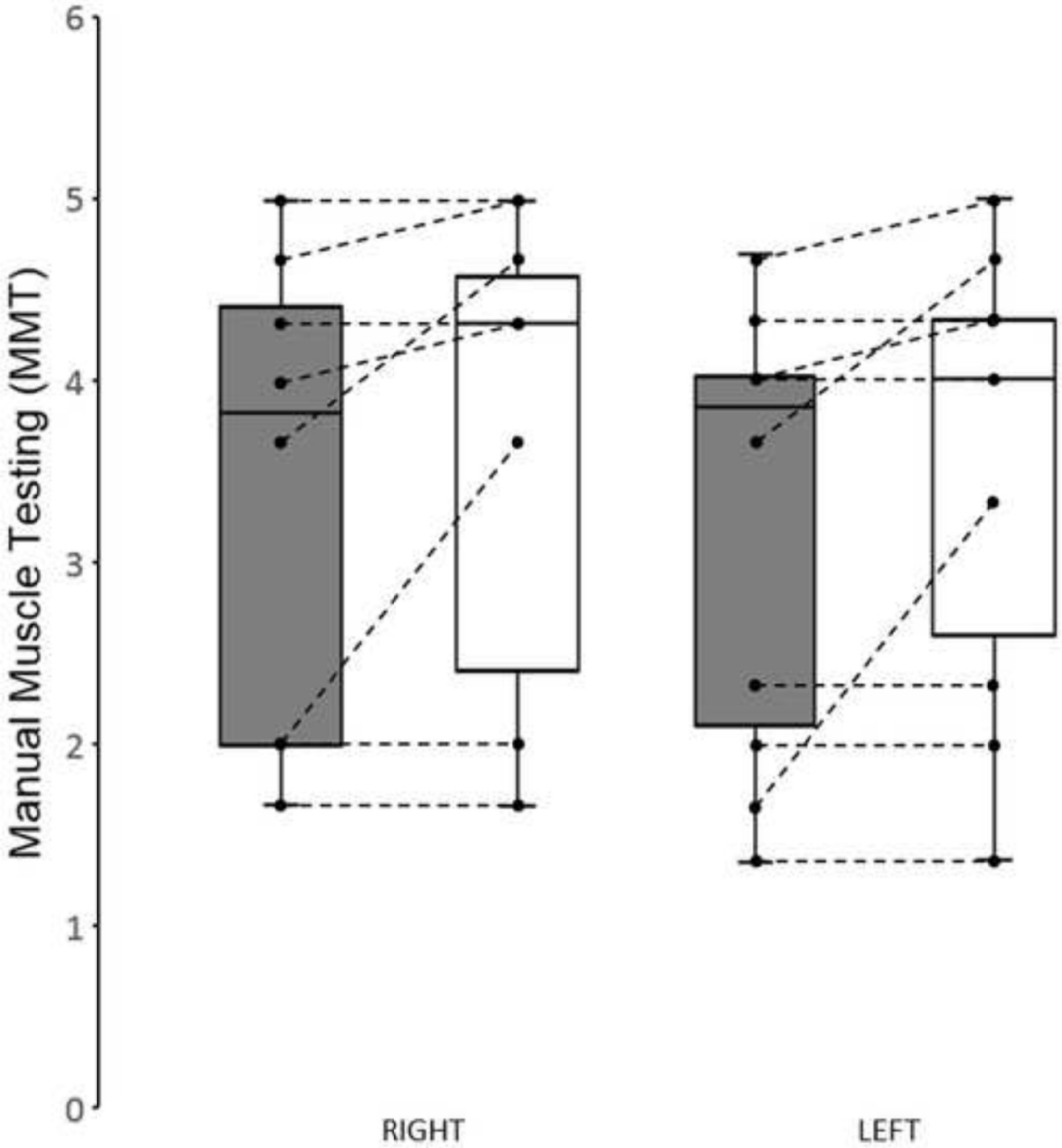
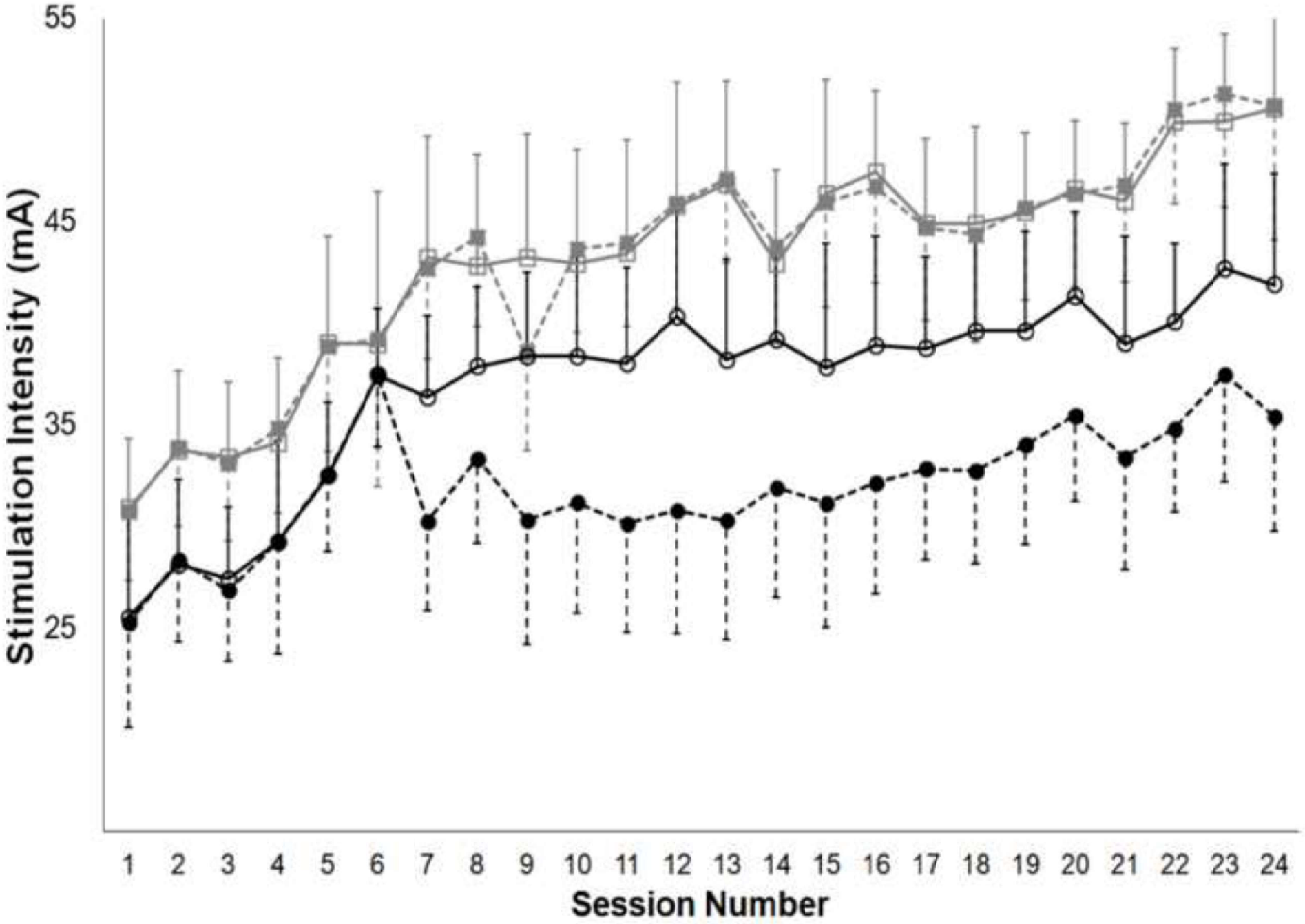


Figure 4


55
45
35
25
Stimulation Intensity (mA)
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Session Number