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# Electrical stimulation for testing and optimizing neuromuscular function in vivo: historical perspective and major advances

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ABSTRACT

This historical review aims to summarize the major advances – particularly from the last 50 years – in transcutaneous electrical stimulation, which can be used either as a tool to investigate neuromuscular function and its determinants (electrical stimulation for testing; EST) or as a therapeutic/training modality to optimize neuromuscular and physical function (neuromuscular electrical stimulation; NMES). We focus on some of the most important applications of electrical stimulation in research and clinical settings, such as for investigating acute changes, chronic adaptations and pathological alterations of neuromuscular function with EST, as well as for improving, preserving and restoring muscle strength and mass with NMES treatment programs in various populations. For both EST and NMES, several major advances converge around understanding and optimizing motor unit recruitment during electrically-evoked contractions, also taking into account the influence of stimulation site (e.g., muscle belly vs nerve trunk) and type (e.g., pulse duration, frequency and intensity). This information is equally important both in the context of mechanistic research of neuromuscular function as well as for clinicians who believe that neuromuscular function optimization is required to provide health-related benefits to their patients.

*Keywords:*
Activation level
Contractile properties
Fatigability
Ageing
Strength training
Rehabilitation

## 1. Introduction

In the last decades, there has been an increasing interest in human neuromuscular function, as well as the ensuing functional and health-related repercussions (such as on mobility and quality of life). Neuromuscular function can be defined as the capability of a muscle to generate force/power while considering the underlying neural and muscular determinants (such as voluntary activation (VA) and contractile properties) (Fig. 1). A major focus for many researchers and clinicians worldwide has been understanding neuromuscular function through the *in vivo* evaluation of its determinants and also improving neuromuscular function with clinically-implementable strategies.

Application of electrical stimuli to the skin overlying a muscle or a nerve trunk (i.e., transcutaneous electrical stimulation (TES)) can induce "involuntary" muscle contractions. The characteristics of these contractions (such as contraction speed and force) can inform some of the determinants of neuromuscular function. Repetition of these contractions – in the form of a structured treatment program with trains of stimuli – could help to promote neuromuscular and functional improvements. Therefore, TES is an incredibly powerful tool both for researchers who are interested in the objective evaluation of neuromuscular function and for clinicians who believe that neuromuscular function optimization is required to provide functional and health-related benefits to their patients.

Given the methodological challenges of interpreting neuromuscular output during volitional muscle contractions, TES has increasingly been used to investigate *in vivo* neuromuscular function in humans. We refer to this type of TES, which is mostly applied over a nerve trunk or muscle belly as a single/double pulse with supramaximal current intensity (even if submaximal trains of pulses can also be used), as electrical stimulation for testing (EST). Specifically, although EST (and TES in general) cannot replicate the natural muscle activation pattern that occurs with descending voluntary drive, it can provide insights about intrinsic contractile properties, neural excitability, and the capacity of the central nervous system to maximally activate a muscle. These insights not only allow one to track acute or chronic changes in neuromuscular function within a group of participants, but they allow inter-group comparisons; for example, one could explore age-related differences or disease-specific alterations. Another type of TES that is designed to be applied repeatedly as a training stimulus is neuromuscular electrical

stimulation (NMES), also referred to as functional electrical stimulation (when it is used to generate a movement rather than a contraction) or electromyostimulation. NMES, which is generally applied over the muscle belly with relatively long pulse trains, with frequencies that generate a tetanic contraction of moderate force, and with submaximal current intensities, has long been used as a treatment modality in clinical settings. Nowadays, NMES is largely employed as a complement or as a substitute to conventional treatment programs, with the goal to improve, restore or preserve neuromuscular function of a variety of patient and participant populations. EST and NMES share several methodological and physiological principles that have evolved significantly in the last decades and their use (and combination) in both research and clinical settings is growing.

This review presents important technical and neurophysiological aspects of EST and NMES as well as their applications, with a historical perspective on major advances, particularly from the last 50 years. Specifically, the first section focuses on EST as a tool for investigating acute changes (such as fatigability), chronic adaptations (such as those associated with ageing) and pathological alterations of neuromuscular function, with particular emphasis on its determinants (Fig. 1, left). The second section is devoted to the clinical use of NMES as a treatment modality for improving (e.g., for healthy individuals), preserving (e.g., for partially/totally immobilized individuals) and restoring (e.g., after surgery) neuromuscular function, with special emphasis on functional and health-related consequences (Fig. 1, right).

[FIG. 1 ~HERE]

## 2. EST for investigating neuromuscular function

### *2.1. Technical aspects and underlying physiology of EST*

In the context of mechanistic research of neuromuscular function, the two most common forms of EST are stimulation over a peripheral nerve or stimulation over the muscle belly. With several parameters to manipulate (e.g., stimulation frequency, pulse width and number, electrode number and size, etc.), these forms of EST are highly customizable to the research question. The order of motor unit (MU) activation is dependent on both proximity to the electrodes and the axonal diameter. This is true whether the stimulation depolarises axons (nerve EST) or axonal branches (muscle belly EST). As such, it is widely believed that EST (and TES in general) does not activate MUs according to size/type (Gregory and Bickel, 2005; Jubeau et al., 2007).

With nerve EST, regardless of the order of MU activation, the current can be increased until all axons have been depolarized; that is, there is a plateau of the compound muscle action potential (M-wave) or the force response to a single stimulus (twitch). The ability to activate all muscle fibres is particularly useful for the interpretation of *in vivo* neuromuscular function, including changes with an intervention.

In contrast to nerve stimulation, muscle belly EST is unlikely to activate all MUs, due to the position of the electrodes relative to the muscle fibres and the need to limit current output to prevent contraction of antagonist muscles. This distinction makes nerve EST the ideal option, but, depending on the muscle/muscle group of interest and the stimulation parameters (e.g., single pulse vs. train), there are many circumstances when muscle belly EST is superior.

A third, less common form of EST, corticospinal tract stimulation, also warrants a brief discussion because it is a highly valuable technique to study acute changes in neural excitability. Depending on the muscle group of interest, stimulation is applied at the level of the mastoids/cervicomedullary junction (Ugawa et al., 1991), the thoracic spine (Martin et al., 2008), or lumbar spine (Skarabot et al., 2019). As the stimulation is delivered subcortically, the evoked response indicates motoneuronal excitability, provided one also records the maximal M-wave to control for possible changes in peripheral excitability. Further, if both corticospinal tract and transcranial magnetic stimulation of the motor cortex are used, comparison of the responses enables insight into

the cortical contribution to the motor evoked potential elicited by transcranial magnetic stimulation (Taylor and Gandevia, 2004).

The origins of TES can be traced to 1802 (see also Table 1) when Giovanni Aldini built on Galvani's 1791 description of "animal electricity" to elicit muscle contractions with the application of electricity to recently deceased humans (in (Parent, 2004)). The first seminal work with TES to test neuromuscular function is Angelo Mosso's *La Fatica*, which was published in 1891 (in (Di Giulio et al., 2006)). Although these experiments focused on the study of muscle fatigue (see section 2.2), they still laid the foundation for various present-day uses of EST. Perhaps the most influential work to involve TES for the study of neuromuscular function was Merton's publication in 1954 (Merton, 1954b). In those experiments, Merton introduced several fundamental concepts for neuromuscular testing, including the interpolated twitch technique to determine if muscle fibres can voluntarily be made to contract maximally.

Among the articles worth highlighting from the last 50 years, we will turn our attention to a series of studies published in the late 1970s by the group of Jones, Edwards, Bigland-Ritchie, and others. In the first article, Edwards and colleagues (Edwards et al., 1977) discovered that the recovery of tetanic force after fatiguing contractions is dependent on the stimulation frequency. Specifically, force recovered rapidly when tested with a high frequency (100 Hz) but remained impaired for many hours when tested with a low frequency (20 Hz). This phenomenon became known as *low-frequency fatigue*, but the preferred terminology is now *prolonged low-frequency force depression* (Allen et al., 2008). Comparison of low-to-high frequency responses was a critical advancement because it enabled indirect insight into causes of force loss after fatiguing contractions, and also highlighted the possibility of drawing an oversimplified view of contractile capacity if one uses a single frequency of EST to assess the neuromuscular function. Two years later, the importance of stimulation frequency was demonstrated in another way, when prolonged, continuous TES was used to induce fatigue (Bigland-Ritchie et al., 1979; Jones et al., 1979). These companion articles contrasted mechanical and electrical responses during a prolonged maximal voluntary contraction (MVC) to responses evoked by prolonged ETS at a low (20 Hz) or high frequencies (50-100 Hz). Although high frequencies of stimulation evoked a much greater initial force, the magnitude and rate of force loss was considerably greater compared to the low-frequency condition, which had minimal force loss (Jones et al., 1979). M-wave recordings revealed that electrical

propagation was preserved at 20 Hz, but had marked failure with each increase in frequency (Bigland-Ritchie et al., 1979). This phenomenon of *high-frequency fatigue* is a considerable issue for the design of stimulation protocols for clinical/rehabilitative purposes (NMES), when the aim is to minimise participant discomfort but maximise the training load (see section 3).

[TABLE 1 ~HERE]

### *2.2. Acute changes in neuromuscular function*

As described later in this subsection, most of the research that uses EST to assess acute changes in neuromuscular function is focused on impairments induced by exercise (Table 2). However, EST can also reveal important positive adaptations such as muscle potentiation. Enhanced twitch tension following tetanic stimulation was reported for animal muscle in 1858 by Moritz Schiff (in (Botelho and Cander, 1953)), but this post-tetanic potentiation was not documented for human muscle until 1953 (Botelho and Cander, 1953). Further, another 30 years passed before the phenomenon of twitch potentiation was explored after voluntary contractions. Vandervoort and colleagues (Vandervoort et al., 1983) confirmed, in humans, the influences of muscle length and muscle fibre type on potentiation, and also revealed that 10 s appears to be the optimal duration for a conditioning MVC. Contractions longer than 10 s tended to reduce the magnitude of potentiation due to the competing effects of fatigue (for review, see (Rassier and Macintosh, 2000)). Twitch potentiation reflects calcium-dependent phosphorylation of myosin light chains (Persechini et al., 1985), which means EST-derived measures of potentiation provide indirect insight into calcium handling within the muscle.

Dating back to the work of Mosso (1891), TES has held a pivotal role in the study of neuromuscular fatigability and the subsequent recovery thereof. As recognised by Mosso, involuntary activation of muscle permits the investigation of fatigue without "participation of the will", which led to concepts of peripheral and central fatigue. Mosso believed that repetitive muscle stimulation excluded the possibility of fatigue within the brain or nerves, but, based on work primarily from Collins and colleagues over the last ~15 years, it is now known that muscle belly TES may lead to some force development via activation of Ia afferents (Bergquist et al., 2011). The central contribution to force production is much greater for TES over the nerve (Bergquist et al., 2011), and, at either

site, can be enhanced by a longer pulse duration and higher frequency of stimulation (Collins, 2007). As such, depending on the research question, careful consideration is needed to select the optimal EST location and parameters.

Although TES is used to induce fatigue in the manner introduced by Mosso in 1891, the vast majority of studies to investigate peripheral fatigue with EST compared responses evoked prior to a volitional exercise task to responses collected during or after the task (Millet and Lepers, 2004). Because it involves minimal discomfort for the participant and is not influenced by central mechanisms, the most common index of peripheral fatigue is the force response to delivery of a single pulse when the muscle is relaxed; i.e., the resting twitch. However, given that exercise can often lead to a disproportionate force loss at low compared to high frequencies (Allen et al., 2008), the resting twitch likely overestimates any impairment of muscle contractility. Similarly, if the number of pulses is too low, even trains delivered at a high frequency can overestimate contractile impairments (Ruggiero et al., 2021). Given these limitations, we believe that the most expedient and physiologically relevant evaluation of muscle contractility in a fatigued state is likely a 1-s train at the frequency that corresponds to the expected mean MU discharge rate at the force level used during the fatiguing task.

Based on the concept of twitch interpolation introduced by Merton in 1954, EST has been used extensively to investigate exercise-induced reductions in VA, i.e., central fatigue. In his seminal study, Merton concluded that VA for adductor pollicis was complete prior to and during a fatiguing MVC (Merton, 1954b). However, with more sensitive measurement techniques, it is now clear that the central nervous system seldom fully activates a muscle/muscle group, and most forms of fatiguing exercise will lead to a reduction in VA (Gandevia, 2001). The presence of an EST-induced superimposed twitch during a MVC indicates that there is incomplete recruitment of spinal motoneurones, a failure to discharge motoneurones at the rate necessary to develop maximal tension, or a combination of both mechanisms (Belanger and McComas, 1981). As EST of a nerve or muscle belly does not pinpoint the site(s) responsible for incomplete activation of the muscle, for suitable muscle groups, transcranial magnetic stimulation can be used to identify if there is suboptimal output from the motor cortex (Todd et al., 2003). Moreover, although it does not relate to VA per se, EST of the corticospinal tract reveals that fatiguing exercise leads to an activity-dependent reduction in motoneurone excitability (McNeil et al., 2011), which likely contributes to central fatigue (McNeil et al., 2009).

Another area that has benefited greatly from EST is the study of acute exposure to environmental stressors, such as heat, cold, or hypoxia. In the early 1980s, Davies and colleagues established that *in vivo* measurements of plantar flexor contractile properties were sensitive to changes in muscle temperature (Davies et al., 1982; Davies and Young, 1983). Specifically, a reduction of muscle temperature slowed contraction and relaxation times, and markedly reduced twitch force; whereas, elevated muscle temperature led to faster contraction and relaxation times but had no effect on twitch force. With acute exposure to hypoxia, EST has demonstrated an impairment of VA (McKeown et al., 2020), but this is not always the case (Jubeau et al., 2017). When fatiguing exercise is performed, it is reported in nearly all studies that hypoxia exacerbates peripheral fatigue (Ruggiero et al., 2020) but does not affect central fatigue measured with EST (Rupp et al., 2015). Of note, when central fatigue is measured using transcranial magnetic stimulation, hypoxia typically leads to a greater reduction of VA compared to normoxia (Goodall et al., 2012; Ruggiero et al., 2018).

[TABLE 2 ~HERE]

### *2.3. Chronic changes in neuromuscular function*

Given the marked adaptations that can occur within the neuromuscular system, EST has proven to be an essential technique for the non-invasive investigation of neural and contractile changes associated with more chronic events (i.e., days up to years or even decades) such as disuse, training, and healthy aging (Table 2). The first large-scale study using EST to investigate possible age-related changes in contractile properties and neural drive was conducted by Vandervoort and McComas (Vandervoort and McComas, 1986), who examined dorsiflexor and plantar flexor function in healthy, active females and males between 20 and 100 years of age. Using single-pulse EST, it was determined that VA did not decline with age, but there were progressive reductions of twitch force and speed, the magnitude of potentiation, and maximal M-wave amplitude. From these data, the authors concluded that the age-related reduction of MVC force was due entirely to a loss of excitable muscle mass. More recent data also implicated muscle quality as a contributor to the age-related reduction of strength and power (McNeil et al., 2007), but the majority of subsequent studies support the conclusions that older adults can achieve the same VA score as young adults, and there is an age-related slowing of contractile properties.

When EST is applied as a train of pulses rather than a single stimulus, this age-related slowing leads to a leftward shift of the force-frequency relationship (Narici et al., 1991), but mixed results with a fatiguing protocol. Stimulation frequency is likely to explain the mixed findings, as fatigability is often reported to increase with age when EST is delivered at 10-20 Hz (Davies and White, 1983), but to be unaltered (McPhee et al., 2014; Stevens et al., 2001) or decrease with age at higher frequencies (≥30Hz) (Narici et al., 1991). Compelling evidence for the crucial role of stimulus frequency was provided by Allman and Rice (Allman and Rice, 2004), when they examined possible age-related differences in fatigability of the quadriceps to two different protocols: i) 14.3 Hz, and ii) the frequency that evoked 60% of an individual's 100 Hz force (14.9 and 12.7 Hz for young and old, respectively). Force loss was not different between the age groups with 14.3 Hz, but was less for old than young when the frequency was normalized to account for the leftward shift of the force-frequency relationship.

Electrical and mechanical responses to EST also provide insights into neuromuscular adaptations to periods of training and disuse. Perhaps it should be unsurprising given the diverse experimental designs used to address these interventions, including the different muscles/muscle groups that have been examined (e.g., hand vs lower limb), but data from studies in both of these areas provide no consensus. In fact, several measures from single-pulse EST (e.g., twitch force and speed, M-wave amplitude and duration, VA) have been reported to increase, decrease, or be unaltered after immobilisation or various forms of strength training (Campbell et al., 2019; Duchateau and Enoka, 2002; Folland and Williams, 2007; James et al., 2021; Shield and Zhou, 2004). Besides the use of EST to investigate neural and muscular adaptations induced by volitional training, TES has also been applied as the training stimulus, when it is referred to as NMES (see section 3).

### *2.4. Pathological alterations in neuromuscular function*

Although neuromuscular diseases or neurological conditions typically have an initial insult within the nervous system, there is a subsequent opportunity for adaptations at multiple sites throughout the motor pathway. EST enables one to identify and localise any adaptations. For example, EST during a MVC has been used to identify that neural drive to the muscle (VA) is impaired after a stroke (Klein et al., 2010), and in persons with amyotrophic lateral sclerosis (ALS) (Sharma et al., 1995), multiple sclerosis (see (Mamoei

et al., 2020) for review), or Parkinson's Disease (Folland et al., 2011; Stevens-Lapsley et al., 2012a). Moreover, EST has identified that several of these conditions also lead to altered contractile properties, including slowed muscle relaxation for persons with ALS (Sharma et al., 1995) and multiple sclerosis (Ng et al., 2004), but faster contraction and relaxation for persons with a spinal cord injury (SCI), albeit with a surprising leftward shift of the force-frequency relationship (Gerrits et al., 1999).

Among the many excellent studies conducted in a variety of clinical populations (see also Table 2), we will focus on a couple with unique applications of EST. In 2015, Prak and colleagues conducted one of the few investigations of fatigability during a volitional task in persons with an incomplete SCI (Prak et al., 2015). The authors used the interpolated twitch technique to assess neural drive to the first dorsal interosseous muscle during brief MVCs and a sustained (2-min) MVC, but corrected the superimposed twitch for SCI-related effects. Based on this novel approach, it was concluded that corticofugal drive was not impaired relative to controls during brief MVCs; however, despite no group difference for force loss during the 2-min MVC, persons with a SCI had greater central fatigue but lesser peripheral fatigue than controls.

In 2007, Vucic and colleagues (Vucic et al., 2007) used repetitive stimulation of the median nerve and a computerized threshold-tracking program to explore the possibility that peripheral factors contribute to the greater fatigability reported for persons with ALS compared to controls (Sanjak et al., 2001). A sustained 1-min MVC of abductor pollicis brevis led to greater activity-dependent axonal hyperpolarization for persons with ALS, which indicates greater peripheral fatigability compared to controls. The authors speculated that ALS-mediated loss of MUs would require greater discharge rates in surviving MUs, thereby leading to greater activity-dependent impairments of axonal excitability relative to controls. In summary, EST has been instrumental in helping us begin to understand the underpinnings of alterations in neuromuscular function with disease or neurological conditions.

## 3. NMES for neuromuscular training/rehabilitation

### *3.1. Technical aspects and physiological specificities of NMES*

Fig. 2 summarizes the four main steps characterizing the modern application of NMES in a sort of semi-closed loop approach, where various physiological data relative to the characteristics (step 2) and consequences (step 3) of the evoked contraction are used to refine technical features of NMES (step 1) mainly in relation with current, electrode and general setup characteristics. The ultimate goal of this process is to optimize treatment effects of NMES (step 4). From an historical perspective (Table 3), a predominantly "methodological development" phase (starting from the 1980s) can be distinguished from a subsequent predominantly "physiological application" phase (starting from the 1990s).

[FIG. 2 ~HERE]

Since the pioneer studies of Morendo-Aranda and Seireg (Moreno-Aranda and Seireg, 1981a, b), the major goal of several methodological investigations has been to examine the impact of selected current and electrode characteristics on two main variables: evoked force and self-reported discomfort/pain. Evoked force is generally quantified as the amount of force generated by NMES as a percentage of the MVC force, while self-reported discomfort/pain is usually evaluated with numerical, verbal, or visual analogue scales. In fact, NMES treatment effectiveness has repeatedly been suggested to be improved by increasing the level of evoked force (Selkowitz, 1985; Stevens-Lapsley et al., 2012b) and also by decreasing the level of discomfort (Delitto et al., 1992). Such a "quest" for the optimal NMES parameters has nevertheless been quite inconclusive – except for the crucial importance of motor point localization (Gobbo et al., 2011; Gobbo et al., 2014) – mainly due to the vast heterogeneity of materials and procedures, in addition to the considerable inter-muscle and inter-subject variability. An example is the endless controversy around the presumed superiority of alternating (such as "Russian") current against pulsed currents, which has never been confirmed, despite multiple trials (Laufer and Elboim, 2008; Vaz and Frasson, 2018). Together with a better knowledge of the neurophysiological bases of NMES, this led Lieber and Kelly (Lieber and Kelly, 1991) to suggest that externally-controllable factors such as stimulation current or electrode size could not be considered as the main determinants of evoked torque, while intrinsic

muscular properties such as the density and orientation of motor nerve branches – particularly in relation with the stimulating electrodes (Knaflitz et al., 1990) – are crucial. These timely observations have opened the door to a new physiological approach to NMES.

Similar to EST, NMES has become a laboratory model to explore previously-neglected central and peripheral nervous system contributions to contractions evoked by pulse trains, including MU recruitment pattern (see also section 2). It has long, but wrongly, been believed that a systematic reversal in recruitment order would occur during NMES of human muscles, similarly to animal models, and also that the nervous system would be largely bypassed by the peripheral stimulation. Since the influential review of Gregory and Bickel (Gregory and Bickel, 2005), it is commonly accepted that NMES recruits MUs in a non-selective (disorderly), spatially-fixed (rather superficial) and temporally synchronous (dictated by stimulation frequency) pattern. These features basically explain most of the acute physiological responses to NMES (e.g., metabolic stress, fatigability, muscle damage), with a non-negligible muscle- and parameter-specific involvement of spinal (Collins et al., 2001) and supraspinal (Smith et al., 2003) centres. From a neural perspective, NMES seems to even have an effect that is not accessible by voluntary activation (e.g., contralateral facilitation; (Howard and Enoka, 1991)). Over the last two decades, an emerging trend is represented by the technologically driven development and validation of NMES paradigms that may recruit MUs in a (pseudo) physiological manner, thereby maximizing spatial recruitment and minimizing fatigability. Some of these options include wide-pulse NMES (Collins, 2007; Collins et al., 2001), spatiotemporally distributed NMES (Malesevic et al., 2010; Popovic and Malesevic, 2009) and interleaved muscle belly-nerve trunk NMES (Lou et al., 2017).

[TABLE 3 ~HERE]

### *3.2. NMES to improve neuromuscular function in healthy subjects/athletes*

NMES has initially been used for preventing disuse muscle atrophy and weakness caused by denervation (Jackson and Seddon, 1945; Osborne, 1951) (Fig. 3) and subsequently by joint injury (Williams and Street, 1976). Only since the 1970s-1980s it has been applied to non-injured athletes and even to non-athletic individuals (including healthy elderly people) to complement conventional training and fitness programs (see

Table 4). Actually, the well-known studies of Yakov Kotz (presented at a conference in 1977; in (Ward and Shkuratova, 2002)) do not correspond to the first application of NMES training for healthy individuals, as in fact the pioneering, though less considered, study dates back to 1965 (Massey et al., 1965). Kotz was considered responsible of exaggerated and unfounded claims, probably because he never published his findings in English, despite the fact that similar results were obtained by others (e.g., (Delitto et al., 1989; Selkowitz, 1985)). In all cases, such spectacular findings have generated a substantial amount of interest that is reflected by the large number of NMES training studies conducted in healthy subjects and athletes in the 1980s-1990s-2000s (Gondin et al., 2011; Seyri and Maffiuletti, 2011). However, most of these studies suffer from poor methodological and reporting quality (as an example, few randomized controlled trials have been conducted and a sham condition is extremely rare), which could have led to biased results besides the large interindividual variability discussed in the previous subsection. The meta-analysis published by Bax et al. (Bax et al., 2005) has definitely closed the polemic around the presumed superior effectiveness of NMES training for improving unimpaired muscle strength, by demonstrating that it is in fact less effective than voluntary strength training.

The rationale for introducing NMES as a complement to classical training programs in athletes but also in healthy elderly individuals is weak for several reasons: limited muscle recruitment, poor functionality, and muscle soreness. In addition, there is an argument that NMES could promote further neuromuscular adaptability thanks to a new training stimulus/stress. There are two unique aspects of NMES that give partial support to this argument: the possibility to activate some fast muscle fibres at relatively low force levels (Gregory and Bickel, 2005) and the chance to induce some neural adaptations (e.g., cross education) that are different from and probably complementary to those induced by conventional strength training (Hortobagyi and Maffiuletti, 2011; Hortobagyi et al., 1999). Besides these interests in NMES for potentially improving the neuromuscular function of healthy subjects, it is important to remember that a chronic low-frequency model of NMES training (4 hours/day during 10 weeks) similar to those used in animals has improved the aerobic-oxidative capacity and induced a fast-to-slow shift of muscle fibre type distribution in healthy volunteers (Nuhr et al., 2003). On the other hand, the recent introduction of low-frequency NMES for improving post-exercise recovery in athletes (Babault et al., 2011) as well as whole-body NMES (usually referred to as whole-

body electromyostimulation) for health and performance (Pano-Rodriguez et al., 2019) could be seen as industry-driven applications not fully supported by a theoretical framework and therefore prone to possible side effects (Teschler and Mooren, 2019).

[TABLE 4 ~HERE]

### *3.3. NMES to preserve/restore neuromuscular function in various patient populations*

Periods of injury or illness often result in an episode of muscle disuse. Experimental disuse in otherwise healthy individuals leads to an approximate muscle atrophy of 0.5-0.9% per day, which is accompanied by a ~2- to 3-fold greater reduction in muscle strength (Deschenes et al., 2002; Wall and van Loon, 2013). The loss of neuromuscular function occurs to a proportionally greater extent in the first few days following the removal of muscle contraction, when decreases in muscle size are often not yet measurable. Moreover, these losses of muscle strength and size are accompanied by changes in both peripheral and central determinants of neuromuscular function (Clark et al., 2008; McComas, 1994). Factors that have been demonstrated to affect the loss of muscle mass and neuromuscular function include the cause for and duration of immobilization, the number of joints immobilized, the length at which a muscle is immobilized (Tabary et al., 1972), and the age of individuals undergoing disuse (Deschenes et al., 2008). Yet, a large part of the observed deterioration is thought to be due to the removal of contraction at the muscle level. As such, the reintroduction of contractions via NMES has been implemented as a strategy to preserve neuromuscular function during disuse.

Interestingly, various models of experimental bedrest have been used in healthy volunteers to simulate conditions of microgravity experienced during spaceflight (Narici and de Boer, 2011). With astronauts experiencing large degrees of muscle atrophy despite extensive exercise programs conducted in orbit, Duvoisin and co-workers demonstrated in 1989 that NMES attenuated reductions in leg volume and strength during 30 days of bedrest simulating microgravity (Duvoisin et al., 1989). Although for obvious reasons it is difficult to conduct sham-controlled studies during spaceflight, and quantifiable data are limited (Mayr et al., 1999), a case study from 2015 demonstrated that NMES use with the Hybrid Training Station during the final 4-week period at the International Space Station attenuated upper arm muscle loss, but did not affect the decline in muscle strength (Shiba

et al., 2015). These as well as other findings (Maffiuletti et al., 2019) support the application of NMES in space whilst highlighting the need for further evidence of its effectiveness.

NMES has been used in various clinical populations undergoing periods of physical inactivity (Jones et al., 2016; Nussbaum et al., 2017); see Table 4). Early work by Eriksson and Häggmark (Eriksson and Haggmark, 1979), and several years later by Gibson and co-workers (Gibson et al., 1988), used NMES via a window in plaster casts to demonstrate NMES can improve muscle function and maintain muscle mass, likely via stimulation of muscle protein synthesis, during 5-6 weeks of immobilization following ACL reconstruction (Eriksson and Haggmark, 1979) and tibia fracture (Gibson et al., 1988). Work in healthy volunteers in the 1980s (Gould et al., 1982), as well as more recently (Dirks et al., 2014), corroborated the positive effect of NMES on muscle mass during experimental disuse, and extended on those findings by demonstrating that NMES did not prevent muscle weakness ((Dirks et al., 2014), in contrast to previous work employing longer-term, whole-body disuse (Duvoisin et al., 1989)). Although a disadvantage of applying NMES through a cast window could be that motor point identification (Gobbo et al., 2011) is not always possible due to limited accessibility, the application of NMES is considered to be beneficial for muscle mass maintenance when compared to no treatment in patients undergoing disuse. These findings extend to more severe situations of disuse due to illness, i.e., intensive care unit patients, who in a seminal 1987 paper were shown to benefit from twice-daily NMES (Bouletreau et al., 1987). Follow-up work in this area extended on these findings by demonstrating the effectiveness of NMES in preserving muscle mass in intensive care unit patients (Dirks et al., 2015; Gerovasili et al., 2009; Weber-Carstens et al., 2013) without adverse systemic effects (Meesen et al., 2010).

Since the application of NMES in immobilized individuals in the 1970s and patients in the intensive care unit from the 1980s onwards (Fig. 3), NMES has also been increasingly considered in patients with advanced disease, such as chronic obstructive pulmonary disease (Vivodtzev et al., 2006; Zanotti et al., 2003) and congestive heart failure (Maillefert et al., 1998; Quittan et al., 2001). In these cases, the goal is to prevent or reverse skeletal muscle wasting for persons who are not able to exercise. In people with chronic obstructive pulmonary disease or congestive heart failure, the use of NMES either alone, or together with conventional exercise training, has been shown to improve

the strength of peripheral muscles, exercise capacity and functional performance, to reduce symptoms, and to improve health-related quality of life.

Mechanistically, although NMES acutely stimulates fasted muscle protein synthesis in individuals with type 2 diabetes (Wall et al., 2012) but not in healthy volunteers (Dirks et al., 2016), more recent work has demonstrated that a single session of NMES following a day of bedrest is able to augment the use of dietary proteins for muscle protein accretion (Dirks et al., 2017). Two studies observed that combining NMES with protein intake during whole-body (Reidy et al., 2017) and local (Zange et al., 2017) disuse had a positive effect on muscle size when compared with neither NMES nor protein, yet the effects on muscle strength are equivocal. Although the individual and combined effects of NMES and protein ingestion are yet to be tested in a disuse setting, the available evidence suggests potential synergistic effects on muscle mass when NMES is timed in close proximity to protein intake. Importantly, although NMES does not appear to protect neuromuscular function during short-term disuse (Dirks et al., 2014; Reidy et al., 2017), given the correlation between muscle mass and strength that is generally observed (Chen et al., 2013), it can be argued that the preservation of muscle mass by NMES during disuse will lead to accelerated recovery of neuromuscular function during rehabilitation from disuse.

NMES has also had favourable effects in patient populations following injury, surgery, or with joint conditions that negatively impact physical function. Early work confirmed that NMES (initially called “faradism”) could be safely applied to patient populations, initially focusing on patients with knee injury (Williams and Street, 1976) and pathology (Johnson et al., 1977). Subsequent research examined the benefits of NMES on patients’ recovery after surgical procedures, such as anterior cruciate ligament reconstruction, and found favourable results. Snyder-Mackler et al. (Snyder-Mackler et al., 1994; Snyder-Mackler et al., 1991) provided some of the strongest early evidence that NMES could attenuate strength loss after anterior cruciate ligament surgery, which translated to improved walking velocity, stance time of the involved limb, and flexion-excursion of the knee during stance compared to voluntary exercise alone. Additional studies with knee and hip osteoarthritis patients further extended the potential applications of NMES (Suetta et al., 2008; Talbot et al., 2003). While the benefits of NMES in people with knee osteoarthritis are a bit more mixed (Bruce-Brand et al., 2012; Imoto et al., 2013; Rosemffet et al., 2004), there seems to be some potential for an effective implementation of NMES, although many of these studies have methodological limitations

(randomization methods not fully described, sample size and power not calculated, lack of blinding). One of the earlier studies also highlighted the benefits of NMES use at home, which increased access and compliance (Talbot et al., 2003); these are important factors for success since regular use is critical to translation of clinical benefits.

In fact, when clinic-based NMES was first applied in an outpatient setting 4 weeks after total knee arthroplasty, benefits were not apparent compared to a volitional exercise group (Petterson et al., 2009). However, it was not clear whether it was due to the limited volume of NMES application (10 contractions/session with only 2-3 sessions per week), to the timing of the NMES application (starting 4 weeks after total knee arthroplasty), or possibly the combination of both. The extension of this work resulted in the development of a home-based, early application of NMES after total knee arthroplasty with greater NMES volume (2 sessions/day, 15 contractions/session for 6 weeks starting 48 hrs after surgery) (Stevens-Lapsley et al., 2012b). Results demonstrated a robust effect of NMES not only on knee extension strength, but also on functional performance measures through 1 year after knee replacement. Subsequently, clinical recommendations using a structured approach for NMES application after knee surgery were developed by consensus in 2016 (Spector et al., 2016) in which early, high-intensity NMES is advocated for patients who achieve a visible muscle contraction within the first week of implementation. Patients could then transition to voluntary strengthening exercise if quadriceps activation deficits are resolved.

[FIG. 3 ~HERE]

## 4. Concluding remarks

This review provides a historical perspective on the main technical and neurophysiological advances in our understanding of how EST and NMES can improve, support, and preserve neuromuscular function in various populations. The major advances in the past decades are centred around optimizing MU recruitment, taking into account the influence of stimulation site (e.g., muscle belly vs nerve trunk), stimulation type (i.e., pulse frequency and duration), and intensity (i.e., maximal vs submaximal). A distinction was made between EST for acute examination of neuromuscular function and repeated application of NMES for training or rehabilitation purposes. Work employing EST *in vivo* in humans has increased our knowledge on various factors affecting both acute and chronic neuromuscular function, including fatiguability and ageing, which could optimize intervention strategies or countermeasures during periods of neuromuscular deterioration. The treatment effectiveness of NMES was objectively discussed and demonstrated to be high in situations of low voluntary muscle contraction and activation (e.g., complete disuse), with its efficacy declining with increasing background levels of voluntary muscle contraction and activation, and as a result being low in physically active individuals.

This historical review also suggests possible future perspectives of EST/NMES which originate from previous research and recent technological advances. For example, for a better exploration of the neurophysiological specificities of the contractions evoked by EST/NMES, high-density surface EMG decomposition will certainly offer new and exciting insights into MU behavior after (and possibly during) electrically-evoked contractions/responses (see e.g., (Kalc et al., 2022)). From a technical perspective, peripheral magnetic stimulation surely represents a valid alternative to EST (Verges et al., 2009) and possibly also NMES (Kremenic et al., 2004), because of a similar physiological response but with less discomfort, despite technical limitations and high costs. Finally, for improving the clinical application of NMES, the use of novel paradigms that recruit MU in a more physiological/complete manner (wide-pulse, spatially-distributed and interleaved muscle-nerve stimulation) – thus inducing less fatigue – as well as the concomitant application of adjuvant strategies (e.g., voluntary action, vibration, blood flow restriction) are interesting perspectives to compensate for the specific (and limited) muscle recruitment pattern of NMES (Blazevich et al., 2021).

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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**Table 1**

Major methodological and physiological advances of TES/EST for investigating neuromuscular function

| Year | Author | Description |
|---|---|---|
| 1803 | Aldini, in (Parent, 2004) | Demonstration that human muscles contract in response to external application of electrical stimulation |
| 1891 | Mosso, in (Di Giulio et al., 2006) | Repeated stimulation of a nerve or muscle lead to force loss (fatigue) "without participation of the brain" |
| 1954 | (Merton, 1954a) | Even subtle desynchronization of electric volleys decreases the size and duration of a muscle twitch |
| 1954 | (Merton, 1954b) | Delivery of stimulation during a MVC to assess if a person can volitionally activate their muscle to its capacity; force-frequency relationship in human muscle |
| 1977 | (Edwards et al., 1977) | Identified that the recovery of force after severe exercise is delayed for low compared to high frequencies of stimulation (later termed *prolonged low-frequency force depression*) |
| 1978 | (Ismail and Ranatunga, 1978) | Explored the influence of joint position on contractile properties with muscle belly stimulation |
| 1979 | (Bigland-Ritchie et al., 1979) | Established that electrical propagation fails with continuous high-frequency stimulation |
| 1979 | (Jones et al., 1979) | Established that force loss was faster and greater with continuous high- compared to low-frequency stimulation (later termed *high-frequency fatigue*) |
| 1981 | (Marsh et al., 1981) | Explored the influence of joint position on contractile properties with nerve stimulation |
| 1981 | (Belanger and McComas, 1981) | Revealed the non-linear relationship between superimposed twitch torque and voluntary torque at the time of stimulation |
| 1992 | (McKenzie et al., 1992) | Mathematical comparison of the superimposed and resting twitch to quantify voluntary activation |
| 2000 | (Kiernan et al., 2000) | Introduced a computerized threshold-tracking program to explore numerous measures of axonal excitability |
| 2001 | (Collins et al., 2001) | Quantified the central contributions to force evoked by trains of wide-pulse stimuli (evidence of plateau potentials) |
| 2009 | (Popovic and Malesevic, 2009) | Identified, in humans, that multi-cathode TES induced less fatigue than conventional single-cathode TES |
| 2011 | (Bergquist et al., 2011) | Compared central and peripheral contributions to motor unit recruitment with nerve versus muscle belly TES |
| 2014 | (Neyroud et al., 2014) | Identified that wide-pulse-high-frequency TES induced greater fatigue compared to short-pulse-low-frequency TES |
| 2017 | (Lou et al., 2017) | Introduced interleaved muscle belly and nerve TES as a means to mitigate the development of fatigue |

Grey: before the past 50 years. MVC: maximal voluntary contraction. TES: transcutaneous electrical stimulation.

**Table 2**

Major advances in TES/EST applications for investigating neuromuscular function

| Year | Author | Description |
|---|---|---|
| 1982 | (Davies et al., 1982) | Documented the influence of muscle temperature on whole-muscle contractile properties |
| 1982 | (Sale et al., 1982) | Initial assessment of the effects of immobilization on twitch properties in a human muscle |
| 1983 | (Vandervoort et al., 1983) | Identified twitch potentiation after a voluntary conditioning contraction, and recommended the optimal contraction intensity and duration |
| 1983 | (Davies and White, 1983) | Investigated possible age-based differences in fatigability to a repetitive TES protocol |
| 1984 | (Duchateau and Hainaut, 1984) | Compared the effect of isometric vs dynamic strength training on twitch and tetanic contractile properties in a human muscle |
| 1986 | (Davies et al., 1986) | Investigated possible sex-based differences in fatigability to a repetitive TES protocol (age-based differences also assessed) |
| 1986 | (Vandervoort and McComas, 1986) | Large-scale, cross-sectional study of neuromuscular function across the adult lifespan (3rd to 10th decade) |
| 1992 | (Rice et al., 1992) | Identified impaired VA in persons with multiple sclerosis |
| 1995 | (Sharma et al., 1995) | Investigated mechanisms of fatigue in persons with amyotrophic lateral sclerosis |
| 1998 | (Binder-Macleod et al., 1998) | Compared the fatigue-producing properties of variable-frequency trains (brief initial interstimulus intervals to induce the catchlike property of muscle) to constant-frequency trains |
| 1999 | (Gerrits et al., 1999) | Discovered a leftward shift of the force-frequency relationship in persons with a SCI |
| 2001 | (Kawakami et al., 2001) | Initial assessment of the effects of immobilization on VA |
| 2001 | (Harris et al., 2001) | Evaluated twitch tension and VA acutely after a stroke |
| 2002 | (Jakobi and Rice, 2002) | Established the need to provide adequate familiarization for older adults in order to accurately assess VA |
| 2004 | (Allman et al., 2004) | Investigated possible age-based differences in fatigability to constant- versus variable-frequency trains of TES |
| 2004 | (Millet and Lepers, 2004) | Scoping review on the amount and origin of neuromuscular fatigue induced by cyclic endurance exercise |
| 2004 | (Allman and Rice, 2004) | Revealed that subtle differences in stimulation frequency influence the presence or absence of age-related differences in peripheral fatigue |
| 2009 | (Miller et al., 2009) | Evaluated the chronic effects of a stroke on VA |
| 2010 | (Klein et al., 2010) | Combined measures of VA, antagonist activity, and atrophy to determine contributions to stroke-induced muscle weakness |
| 2011 | (Folland et al., 2011) | Identified impaired VA in persons with Parkinson's Disease |
| 2015 | (Prak et al., 2015) | Assessed voluntary drive in persons with an incomplete SCI, and introduced a method to correct the superimposed twitch for SCI-related effects |

| | | |
|---|---|---|
| 2019 | (Ruggiero et al., 2019) | Identified the extent to which the magnitude and duration of PLFFD is underestimated when paired stimuli are used instead of a 1-s train of stimuli |
| 2020 | (Ruggiero et al., 2020) | Used a repetitive TES protocol rather than a resting twitch to investigate how peripheral fatigue is influenced by acute and chronic exposure to hypoxia |

Green: acute changes. Blue: chronic changes. Red: pathological alterations. PLFFD: prolonged low-frequency force depression. SCI: spinal cord injury. TES: transcutaneous electrical stimulation. VA: voluntary activation.

**Table 3**

Major methodological and physiological advances of NMES for neuromuscular training/rehabilitation

| Year | Author | Description |
|---|---|---|
| 1965 | (Vodovnik et al., 1965) | Preliminary investigation of the pain response induced by different NMES currents |
| 1981a,b | (Moreno-Aranda and Seireg, 1981a, b) | First attempts to determine optimal stimulation parameters with regard to discomfort and evoked force |
| 1983 | (Hultman et al., 1983) | Selective activation of intramuscular nerve branches (rather than of muscle fibers) |
| 1985 | (Selkowitz, 1985) | Treatment effectiveness proportional to evoked force during a NMES training program |
| 1986 | (Lloyd et al., 1986) | In depth review of human NMES studies with a particular focus on stimulation parameters |
| 1991 | (Lieber and Kelly, 1991) | Intrinsic quadriceps properties (not externally controllable factors) as determinants of evoked force |
| 1991 | (Howard and Enoka, 1991) | Contralateral facilitation of the homonymous muscle induced by unilateral NMES |
| 1992 | (Delitto et al., 1992) | Treatment effectiveness could be improved by reducing the level of discomfort (or by increasing tolerance) |
| 1993 | (Binder-Macleod and Snyder-Mackler, 1993) | Faster fatigability development during NMES than during volitional contractions |
| 1997 | (Feiereisen et al., 1997) | Non-systematic reversal of motor unit recruitment during NMES |
| 1997 | (Vanderthommen et al., 1997) | Exaggerated metabolic demand in superficial muscle regions during NMES compared to voluntary contractions |
| 2003 | (Smith et al., 2003) | Dose-response relation between NMES intensity and brain activation in specific sensorimotor areas |
| 2005 | (Gregory and Bickel, 2005) | Non-selective, spatially-fixed and temporally synchronous motor unit recruitment pattern |
| 2008 | (Jubeau et al., 2008) | Greater muscle damage, hormonal response and fatigability with NMES compared to voluntary contractions |
| 2011 | (Gobbo et al., 2011) | Further confirmation of the importance of motor point localization |

Grey: before the past 50 years. NMES: neuromuscular electrical stimulation.

**Table 4**

Major advances in NMES applications for neuromuscular training/rehabilitation

| Year | Author(s) | Description |
|---|---|---|
| 1965 | (Massey et al., 1965) | First training study in healthy subjects showing increased muscle girth after 9 wks of NMES |
| 1976 | (Williams and Street, 1976) | NMES (13 sessions) improved strength of weak/atrophied muscles in patients with a variety of knee disorders |
| 1977 | (Johnson et al., 1977) | Quadriceps NMES for 6 wks improved knee extension strength in patients with mild and severe chondromalacia patellae |
| 1977 | Kots (in (Ward and Shkuratova, 2002)) | Substantial strength gains (27-56%) in highly-trained young athletes after 3 wks of NMES ("Russian" current) |
| 1979 | (Eriksson and Haggmark, 1979) | Preserved muscle function and oxidative enzyme activity with NMES applied during post-ACLr immobilization (5 wks) |
| 1979 | (Currier et al., 1979) | Equivalent strength gains (20%) for maximal isometric contractions with and without concomitant NMES |
| 1982 | (Gould et al., 1982) | Partial rescuing of muscle disuse atrophy in healthy subjects during 2 wks of long-leg cast immobilization |
| 1985 | (Selkowitz, 1985) | High interindividual diversity in strength gains (4-74%) after 4 wks of NMES with high evoked forces (91% MVC) |
| 1986 | (Wolf et al., 1986) | Similar improvements in functional measures for dynamic squat exercise with and without concomitant NMES in athletes (6 wks) |
| 1986 | (Singer, 1986) | Preliminary evidence of neural adaptations (EMG activity) after 4 wks of NMES in ACL patients |
| 1987 | (Bouletreau et al., 1987) | Twice-daily NMES for 9 d reduced 3-MH and creatinine excretion in ICU patients, but did not modify nitrogen balance |
| 1987 | (Cabric et al., 1987) | Preliminary evidence of muscular adaptations (biopsy) after 3 wks of NMES |
| 1988 | (Gibson et al., 1988) | In-the-cast NMES (1 h/d) preserved both muscle mass and protein synthesis during 40 d of immobilization (tibia fracture) |
| 1989 | (Duvoisin et al., 1989) | NMES with a newly-developed system attenuated reductions in muscle CSA and strength during 30 d of bedrest |
| 1991 | (Snyder-Mackler et al., 1991) | NMES for 4 wks was more effective than voluntary training to improve strength and gait patterns after ACLr |
| 1994 | (Caggiano et al., 1994) | Strength gains in elderly men (72 yrs) after 4 wks of NMES with greater effects in sedentary than in active subjects |
| 1997 | (Butterfield et al., 1997) | Application of NMES as a post-exercise recovery modality (delayed onset muscle soreness) |
| 1998 | (Maillefert et al., 1998) | Low-frequency NMES for 5 wks increased exercise capacity and gastrocnemius muscle volume in CHF patients |
| 1999 | (Hortobagyi et al., 1999) | Greater cross education with NMES than voluntary strength training (6 wks) |
| 2002 | (Maffiuletti et al., 2002) | Increased voluntary activation (twitch interpolation technique) after 4 wks of NMES |

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|---|---|---|
| 2003 | (Zanotti et al., 2003) | NMES for 28 d improved muscle strength and decreased time needed to transfer from bed to chair in bed-bound COPD patients |
| 2003 | (Nuhr et al., 2003) | Fast-to-slow shift of muscle fiber-type composition after 10 wks of chronic (4 h/d) low-frequency NMES |
| 2003 | (Talbot et al., 2003) | Feasibility of a home-based NMES program of 12 wks for older adults with KOA |
| 2005 | (Bax et al., 2005) | Meta-analytic evidence that NMES is not more effective than voluntary strength training to improve strength |
| 2005 | (Gondin et al., 2005) | Time-course of neural and muscular adaptations during 8 wks of NMES |
| 2009 | (Petterson et al., 2009) | In TKA patients, similar effects of strength training with vs without NMES for 6 wks in an outpatient clinic |
| 2010 | (Kemmler et al., 2010) | First training study with whole-body NMES technology in post-menopausal women (14 wks) |
| 2010 | (Walls et al., 2010) | Pilot study on the compliance and effects of preoperative NMES to improve postoperative outcomes in TKA patients |
| 2012 | (Wall et al., 2012) | NMES for 60 min acutely stimulated muscle protein synthesis in elderly individuals with type 2 diabetes |
| 2012 | (Stevens-Lapsley et al., 2012b) | Substantial and long-lasting effects of home-based high-volume NMES for 6 wks early after TKA |
| 2013 | (Weber-Carstens et al., 2013) | NMES for 12 d during ICU stay increased type II muscle fiber CSA in mechanically-ventilated patients |
| 2015 | (Shiba et al., 2015) | Case study demonstrating that inflight NMES for 30 d attenuated muscle mass but not strength loss on International Space Station |
| 2015 | (Dirks et al., 2015) | Twice-daily NMES for 7 d during ICU stay protected type I and II muscle fiber CSA in critically ill comatose patients |
| 2016 | (Spector et al., 2016) | Criterion-based treatment algorithm to restore neuromuscular function in patients after knee surgery |
| 2016 | (Jones et al., 2016) | Cochrane review about NMES for muscle weakness in adults with advanced disease |
| 2017 | (Reidy et al., 2017) | NMES for 5 d during bedrest combined with protein supplementation preserved thigh lean mass, but not strength in healthy older adults |
| 2017 | (Dirks et al., 2017) | NMES acutely stimulated the use of dietary proteins for muscle protein accretion following 1 d bedrest in healthy older adults |
| 2017 | (Nussbaum et al., 2017) | Critical review and clinical recommendations for NMES for treatment of muscle impairment |

Grey: before the past 50 years. Blue: NMES to improve function. Red: NMES to preserve/restore function. ACLr: anterior cruciate ligament reconstruction. CHF: congestive heart failure. COPD: chronic obstructive pulmonary disease. CSA: cross-sectional area. ICU: intensive care unit. KOA: knee osteoarthritis. NMES: neuromuscular electrical stimulation. TKA: total knee arthroplasty. 3-MH: 3-methylhistidine.

## Figure legends

### Fig. 1

Determinants (left) and repercussions (right) of neuromuscular function. Electrical stimulation for testing (EST) allows to explore neural and muscular properties *in vivo* (i.e., the determinants) while optimization of neuromuscular function with neuromuscular electrical stimulation (NMES) should translate into improved functional and health-related outcomes (i.e., the repercussions).

### Fig. 2

From left to right, the four main steps characterizing the modern application of NMES in a sort of semi-closed loop approach are shown (please refer to the text for a better explanation). Asterisks indicate the variables that have the greatest influence on NMES treatment effectiveness, namely optimal electrode position (through motor point localization), maximization of evoked force and minimization of subjective discomfort.

### Fig. 3

Simplified chronology of the initial attempts to apply NMES as a treatment/training modality by patient/subject population. CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; KOA: knee osteoarthritis; THA: total hip arthroplasty; TKA: total knee arthroplasty.

Figure 1



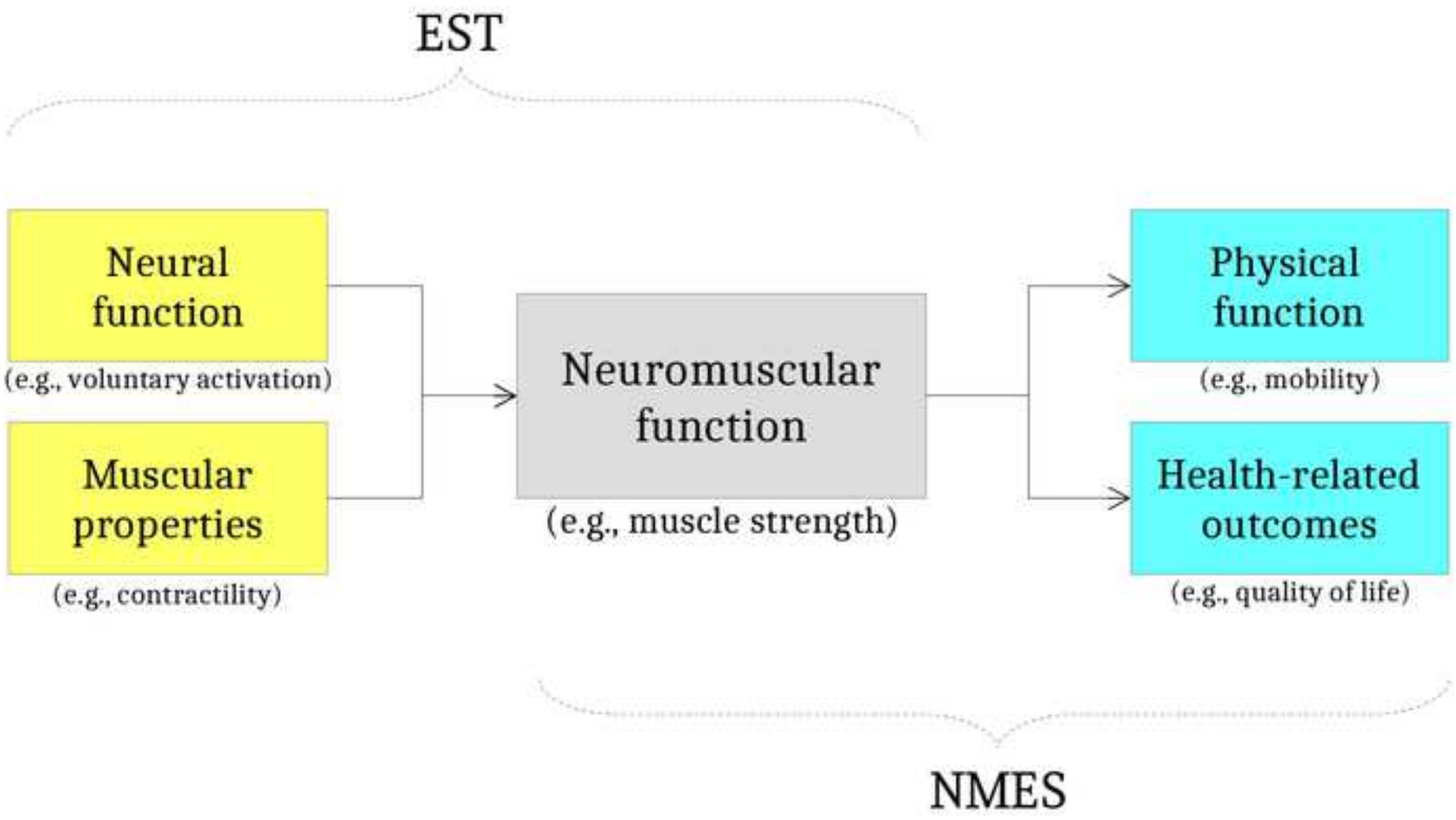

Figure 2



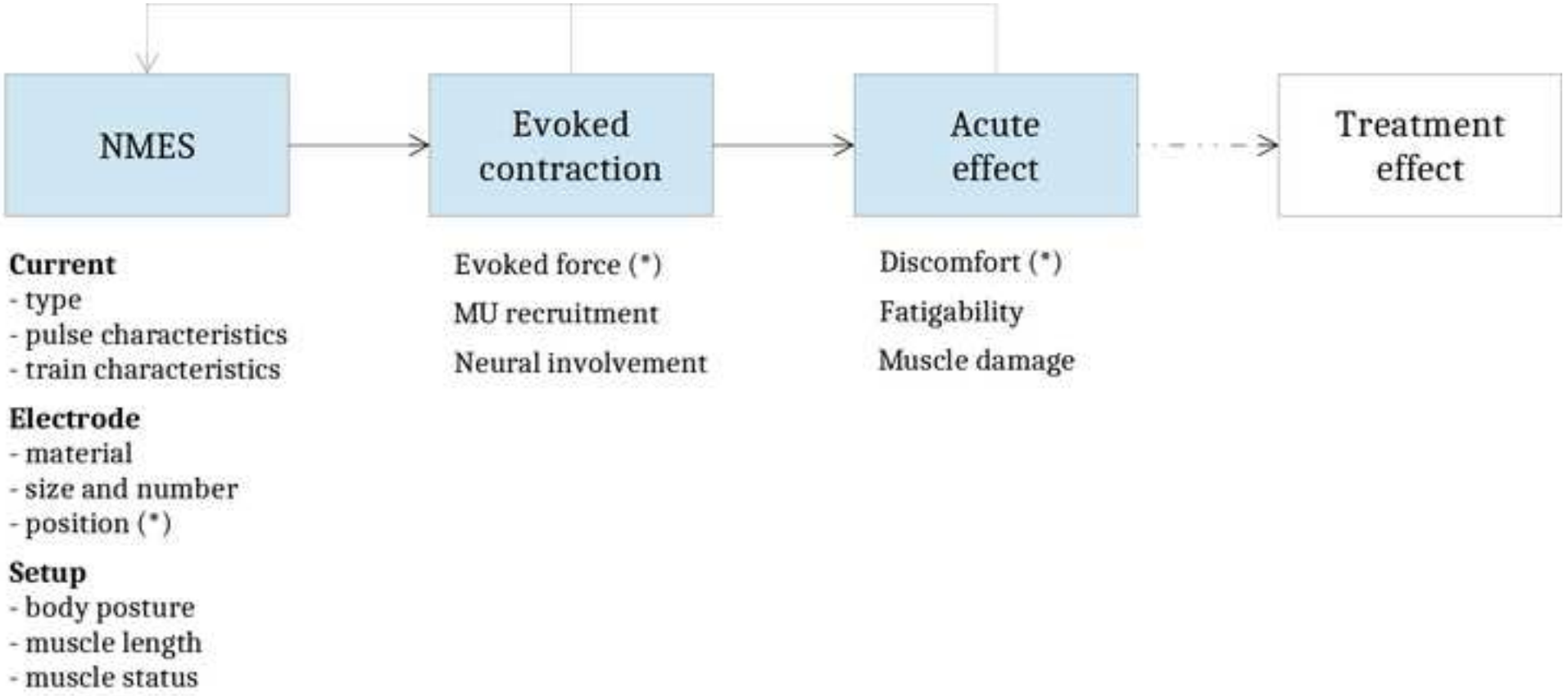

Figure 3