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The use of neuromuscular electrical stimulation (NMES) for managing the complications of ageing related to reduced exercise participation.

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Abstract

Exercise participation and activity levels are low in many older adults, and when paired with the multi-systemic effects of ageing such as sarcopenia and decreased cardiovascular function, can result in a loss of functional independence. Voluntary exercise may not always be feasible for these individuals highlighting a need for alternative therapies. There is a growing body of literature that recognises the positive effects of NMES on muscle strength, muscle mass and cardiorespiratory function in older adults. However, NMES suffers from poor clinical acceptability due to multiple barriers to its use, and poor patient engagement and adherence has been noted. Technology-based supports to exercise, such as biofeedback and gamification have been effectively paired with a variety of rehabilitation interventions. This suggests that these supports could be promising additions to an NMES exercise system to reduce barriers to its use and maximise clinical outcomes.

Keywords: neuromuscular electrical stimulation, ageing, rehabilitation, physical function, technology, sarcopenia

1. Introduction

As the global population ages, the number of older adults who require long term care is rapidly increasing with figures estimated to double by 2050 [1]. This age-related loss of functional independence is associated with chronic and insidious conditions which can negatively alter the neuromuscular and cardiovascular systems. These alterations lead to the progressive loss of muscle mass, strength, aerobic capacity and eventually physical function [2]. The accompanying functional deficits can impair an individual's ability to carry out activities of daily living, and place that individual below a threshold for functional independence [3].

Regular exercise has been shown to delay degenerative processes in senescent muscle [4]. As such, older adults are currently recommended to engage in exercise to prevent morbidity and maintain independence [5]. However, exercise participation is poor in older adults, with those aged 70 - 79 years old 50% less likely than their 50 - 59 years old counterparts to engage in sufficient levels [6]. Although this drop-off in activity levels can in part be linked to factors such as a lack of interest, many older individuals often cannot exercise due to inadequate functional capacity and underlying comorbidities such as pain and chronic illness [7–9]. These limiting factors highlight a need for alternatives to voluntary exercise to reduce the functional deficits associated with age-related alterations in activity patterns [3,10]. Assistive technologies such as neuromuscular electrical stimulation (NMES) have previously been used successfully to target both the neuromuscular and cardiovascular systems in healthy young and older adults and clinical populations [11–13], and could be an effective alternative to voluntary exercise in older adults.

A growing body of evidence demonstrates the efficacy of NMES in athletes and both young and older adults [14–16]. In its current state NMES is used as both a training and rehabilitation

84 tool, and in particular during or after periods of limb immobilisation or disuse [17]. NMES is
85 generally delivered in static positions with no functional movement, differing it from functional
86 electrical stimulation (FES) which is most commonly used in spinal cord injured patients to
87 generate functional movements [18]. However, although NMES can be effective, it does suffer
88 from three main limitations; excessive discomfort, limited spatial recruitment of motor units
89 and the early onset of fatigue due to the high metabolic demand and repeated activation of the
90 same motor units [19]. These limitations can compromise treatment effectiveness. A complete
91 insight into the physiological and methodological considerations of NMES is beyond the scope
92 of this paper and the reader is directed to the following review [19].

93
94 These limitations of NMES have led to the development of a multipath delivery system
95 (multiple current pathways) in combination with the use of larger electrodes integrated into
96 wearable garments (*Figure 1.*) which can disperse current density to allow for higher NMES
97 exercise intensities at a given amount of discomfort [20,21]. This can lead to improved
98 treatment effectiveness, and subsequently better in-patient and home-based exercise and
99 rehabilitation. However, despite these improvements in exercise delivery, NMES currently
100 suffers from poor clinical acceptability [22], and patient engagement and adherence to
101 unsupervised NMES sessions is generally poor. In addition, technology-based exercise
102 supports such as biofeedback and gamification can assist health behaviour change [23,24], and
103 have potential to improve the clinical acceptability of NMES.

(A)

(B)

Figure 1. NMES delivery – (A) electrode positions on the quadriceps and hamstrings; (B) multipath delivery system

Therefore, this review is concerned with the recent progress which has been made in demonstrating the effectiveness of NMES for improving the neuromuscular and cardiovascular systems of older adults and explaining the potential for leveraging digital supports to enhance its implementation. In the first sections, age-related functional and physiological changes will be described. The following sections will give an overview of current exercise recommendations and the application of NMES technologies. Finally, we will discuss how applying supportive digital techniques to create innovative models of NMES delivery could hold promise as therapeutic alternatives to voluntary exercise to attenuate age-related reductions in physical function.

2. Methodology

A literature search was performed in PubMed and Google Scholar with the following key terms: “electrical stimulation” OR “neuromuscular electrical stimulation” OR “electromyostimulation” OR “electrostimulation” AND “ageing” OR “elderly” OR “senior”. A second search used the following terms: “gamification” OR “biofeedback” OR “user-centred design” AND “neuromuscular electrical stimulation” OR “electrostimulation” OR “rehabilitation” OR “exercise”. The search was limited to English language articles

3. Ageing and skeletal muscle structure and function

Sarcopenia, the age-related loss of muscle mass and strength is a hallmark of the ageing process [25], and is seen in 15% to 50% of older adults [26]. Muscle mass loss can range from 3-10% per decade between the ages of 30 and 70 years with this increasing to 15% per decade thereafter [27]. Muscle strength is mostly maintained until 50 years old, where after a decline in strength of 5% per year has been reported [28]. The strength deficits observed in older adults can be explained partly by muscle fibre atrophy although neurological factors such as impaired

muscle activation also likely contribute given that strength is lost 2-5 times faster than muscle mass [26].

Figure 2. Schematic illustrating the order of muscle fiber recruitment during voluntary exercise.

A major driver of muscle fibre atrophy in older adults is altered physical activity patterns. As voluntary muscle activation follows a size order of recruitment (*Figure 2.*) (Type I→Type IIa→Type IIx) [29], higher threshold Type II fibres experience less habitual activation than lower threshold Type I fibres (See *Table 1* for a summary of the characteristics of human muscle fibre types). Intermittent and extended periods of disuse due to reduced activity levels likely contribute to the loss of these powerful muscle fibres and exacerbate physiological changes such as chronic low grade inflammation [30]. In addition, muscle quality is compromised through fat accumulation and fibrosis replacing functional contractile tissue [31],

leading to the loss of the force and power generating capacity of the muscle and compounding muscle mass and strength losses [32].

Table 1. Characteristics of human muscle fiber types

	Type I	Type IIa	Type IIx
Motor neuron size	small	medium	large
Fiber diameter	small	medium	large
Recruitment order	first	second	third
Contraction time	slow	moderately fast	very fast
Force production	low	medium	very high
Fatigue resistance	high	moderate	low
Oxidative capacity	high	moderate	low
Glycolytic capacity	low	high	highest
Metabolism	oxidative	oxidative/glycolytic	glycolytic

Several physiological changes have been linked to sarcopenia. Chronic low grade inflammation is recognised as a likely driver of muscle atrophy in older adults [33] with pro-inflammatory cytokines (e.g. tumour necrosis factor alpha (TNF- α)) increasing the expression of proteins involved in the cells main proteolytic pathway, the ubiquitin proteasome system (UPP), inducing insulin resistance and suppressing the IGF1-PI3K-Akt-mTOR pathway (*Figure 3.*) [34,35]. In addition, inflammation is implicated in alterations to the repair and regeneration capacity of senescent muscle through inflammatory mediated changes in satellite cell function [33]. However, although increased proteolysis likely contributes, a reduction in muscle protein synthesis (MPS) may be more important [36]. In healthy muscle, protein turnover (equilibrium between MPS and muscle protein breakdown (MPB)) is a dynamic process controlled by anabolic signalling pathways e.g. IGF1-PI3K-Akt-mTOR [37,38]. Age-related perturbations in muscle protein turnover, whereby MPB exceeds MPS can lead to the loss of muscle [38]. Anabolic hormones such as testosterone, insulin and IGF-1 are potent activators of the IGF-1

pathway, but their production is reduced in older adults and effects dampened by insulin resistance [39]. In addition, changes in dietary intake and an age-related impairment in the muscle's protein synthetic response to feeding termed "anabolic resistance" also likely contribute to reduced muscle protein accretion [40].

Figure 3. Schematic outlining the IGF-1 signalling pathway. IGF-1, insulin like growth factor-1; PI3K, phosphatidylinositol 3 kinase; Akt/PKB, protein kinase B; mTOR, mammalian target or rapamycin.

4. Ageing and the cardiovascular system

Cardiorespiratory fitness, defined as the ability of the cardiovascular and respiratory systems to provide working muscles with oxygen during sustained physical activity is generally expressed as peak oxygen uptake ($\text{VO}_{2\text{peak}}$) [41], and is considered an independent predictor of future all-cause mortality in older adults [42]. Cardiorespiratory fitness declines progressively with age and is viewed as a strong predictor of functional capacity [43]. Cross sectional studies have observed typical reductions in $\text{VO}_{2\text{peak}}$ of 10% per decade [4,44] whilst a maintenance of 18-20 ml.kg.min^{-1} is reported as being the minimum value required for activities of daily living [45,46]. Thus, an individual's ability to maintain a sufficient level of aerobic capacity will dictate their functional independence.

A reduction in physical activity has been reported to contribute to the age related decline in $\text{VO}_{2\text{peak}}$ [4]. Indeed, when comparing sedentary and endurance trained older males, participating in endurance exercise training attenuated the decline in the age-related losses in $\text{VO}_{2\text{peak}}$ [47]. However, a reduction in exercise levels only appears to initiate the reduction in $\text{VO}_{2\text{peak}}$. Central and peripheral changes such as a reduction in maximal heart rate and a decline in muscle oxidative capacity in response to mitochondrial dysfunction have also both been shown to contribute [48,49], suggesting that interventions which can target central and/or peripheral mechanisms can help attenuate the age-related decline in $\text{VO}_{2\text{peak}}$.

Thus, physical inactivity contributes to reductions in the neuromuscular and cardiovascular systems both directly and indirectly. Inactivity and physiological changes therefore compromise function and can lead to older adults falling below a threshold for independent

living. This increases the number of older adults requiring long term care and highlights the need for interventions to attenuate these degenerative processes.

5. Current exercise recommendations

The American College of Sports medicine (ACSM) currently recommends that over 65's engage in 150mins/week of moderate intensity aerobic exercise, and resistance training (RT) 2x/week to promote and maintain health [50]. The benefits of regular aerobic exercise and RT in older adults are widely recognised [51,52]. Despite this, inactivity amongst the elderly is high. Objective data collected from accelerometers provides alarming results suggesting only 5% of over 65's achieve recommended levels [53]. Whilst lack of time is the most commonly reported barrier amongst younger individuals, older adults cite poor health and a lack of knowledge of the health benefits of exercise [54]. In addition, and owing to multiple comorbidities and the functional deficits associated with the physiological and functional changes of ageing, older adults also face functional barriers such as breathlessness, reduced gait speeds and difficulties rising from a seated position [55,56]. Therefore, current guidelines appear unrealistic and unachievable for many older adults with poor functional independence.

6. Neuromuscular electrical stimulation – an alternative therapy to voluntary exercise?

Neuromuscular electrical stimulation (NMES) involves controlled muscle contractions generated by electrical impulses, which are delivered directly to the target muscle through surface electrodes (*Figure 1.*) and a small, battery operated NMES unit [57]. Commonly stimulated muscles include the quadriceps and hamstrings, and impulses are delivered at high enough intensities to generate visible muscle contractions [17]. Due to its ability to induce fused tetanic contractions, high frequency NMES (HF-NMES) has been used clinically as a tool to preserve or recover muscle mass and function, typically at frequencies of 25 - 100Hz

[19]. In particular, NMES is seen as an effective intervention in stroke rehabilitation for muscle strengthening and motor recovery [58]. Over three quarters of reported strokes, a leading cause of disability worldwide, occur in over 65's and can impair the pathway between upper and lower motor neurons resulting in impaired muscle activation, reduced activity levels and muscle atrophy [59]. Therefore HF-NMES can target not just the primary effects of ageing but also target the complications of underlying comorbidities.

Although the use of HF-NMES is more commonly reported in the NMES literature, a growing body of evidence now supports the use of sub-tetanic low frequency NMES (LF-NMES) to induce cardiovascular adaptations and improve exercise tolerance in a variety of populations with frequency ranges typically between 4Hz - 7Hz [11,60,61]. NMES is a safe intervention, with adverse events rarely occurring and evidence of a constant dose response relationship across studies. Furthermore, due to its portability NMES can be applied unsupervised by the user at home. This makes NMES uniquely placed to help attenuate age-related losses of muscle mass, strength and cardiorespiratory fitness.

6.1. NMES, strength and muscle mass

Recent systematic reviews have concluded that HF-NMES can be an effective and safe strategy to attenuate the age-related decline in muscle strength [15,16]. Interestingly, reports have concluded that NMES can be as effective as voluntary resistance training for improving strength in older adults [13,15,16]. This has been demonstrated after 8 weeks of HF-NMES (25Hz) in older adults, with a significant 15% increase in isometric quadriceps torque [13], which is similar to improvements reported in voluntary exercise studies [51]. This is of clinical interest given that voluntary exercise can be difficult for this population. In addition, several reports have suggested that the effectiveness of NMES is greatest in the most deconditioned

patients [14,16] making HF-NMES a promising intervention to help offset functional impairments associated with ageing in those unable to exercise.

Although HF- NMES is often referred to as a “peripheral” modality with little influence on the central nervous system (CNS), convincing evidence suggests that both neurological (increased muscle activation) and morphological (increased size and number of Type II fibres) factors dictate strength adaptations [62]. The length of NMES intervention appears to dictate the neural and hypertrophic contribution to strength. Gondin et al [62] investigated the effects of NMES on neural drive and muscle architecture and demonstrated significant improvements in isometric muscle torque (+15%) after 4 weeks of HF-NMES (75Hz) with increased muscle activation (+6%) contributing to improvements in healthy young males. Between week 4 and 8 an increase in muscle hypertrophy (+4%) led to further strength gains (+11%) with no significant contribution from increased muscle activation (+1%). In older adults, similar improvements in strength have been reported after 4 weeks of HF-NMES by Caggiano et al [63] (+9%) and Mignardot et al [64] (+26%) respectively, with increased electromyography (EMG) activity suggesting increased muscle activation [64].

Kern et al. [65] reported significant functional, structural and molecular effects in a group of healthy male and female older adults (73.1 ± 6.9 years) after 9 weeks of HF-NMES (60Hz, 2-3x/week). They reported a 6% increase in maximal isometric torque with a concomitant increase in the size (+2.2%) and percentage (+8%) of Type II fibres [65] suggesting that following an increase in muscle activation, increased Type II fibre hypertrophy may be a primary driver of strength adaptations in older adults. A possible reason for the observed hypertrophy may be due to the non-selective and random muscle recruitment pattern of HF-NMES [66]. This aberrant recruitment highlights a significant benefit of HF-NMES in this

population as its use allows for the activation of powerful Type II fibres even at low stimulation intensities [19]. In addition, the authors also reported improved muscle quality. A major contributor to the loss of muscle function is a reduction in muscle quality which is compromised during ageing due to fibrosis and fat accumulation [31]. The authors reported an increase in microRNA-29 [65] (microRNA - small non-coding ribonucleic acids (RNA's) involved in the regulation of gene expression through the degradation or translation suppression of target mRNA's [67]) which is reported to control extracellular matrix (ECM) remodelling in skeletal muscle [68]. Therefore, this increase in microRNA-29 may provide a protective effect potentially counteracting age-related frailty and functional impairments by maintaining muscle quality [65]. This paper by Kern et al [65] demonstrates the most convincing evidence to date of the potential of NMES in this cohort to counteract some of the deleterious effects of ageing.

At the molecular level a single 60 min HF-NMES session has been shown to increase MPS by 27% in senescent muscle [69]. Studies in ICU patients applying NMES for 3-10 days reported similar increases (19.5%) in the phosphorylation of mTOR [70]. Kern et al [65] reported an increase in the expression of IGF-1 and reduced activity of MuRF-1 suggesting that NMES not only regulates anabolic pathways but also modulates muscle catabolism. In addition, NMES may help overcome anabolic resistance in older individuals as even low intensity voluntary contractions may be sufficient to increase the sensitivity of senescent muscle to nutrition [71,72]. Therefore, NMES appears to exhibit positive effects on muscle protein turnover suggesting it may be an effective intervention to help preserve or attenuate age-related reductions in muscle mass.

6.2. NMES and cardiorespiratory fitness

Recently the application of LF-NMES protocols (4Hz) which generate rhythmical muscle contractions, similar to shivering, has been shown to increase oxygen demand in various populations [13,60,73,74]. Banerjee et al [73] reported a 10% improvement in $\text{VO}_{2\text{peak}}$ following 6 weeks of LF-NMES (4Hz, 5x1hr/week) in a middle aged (mean age-48.3 $\pm$ 12.0 yr) sedentary cohort. Similar improvements have also been reported in patients with chronic heart failure [60]. In healthy older adults, modest improvements in aerobic exercise capacity (+3.5%, 6-min walk distance) have been reported following a 6-week (5x 1hr/week) NMES intervention incorporating a low (4Hz, 45 min continuously) and high frequency (25Hz, 15 mins: 5s on/5s off; 15 mins: 5s on/5s off) phase within each 1 hr session [13]. Therefore, repeated application of low frequency NMES over a period of 6-weeks appears to improve exercise tolerance.

Improvements in cardiorespiratory fitness following voluntary aerobic exercise have been linked to central and peripheral adaptations. The impact of central adaptations on cardiorespiratory fitness improvements following LF-NMES are unclear [75]. However, peripheral adaptations like those observed following voluntary aerobic exercise such as an increase in the content of oxidative enzymes (i.e. citrate synthase) have been reported [76]. In addition, increased phosphorylation of 5'AMP activated protein kinase (AMPK), which regulates cellular metabolism and can control the activity of PPAR gamma co-activator 1 alpha (PGC 1 α), the master regulator of mitochondrial biogenesis [77] has been demonstrated after acute and chronic low frequency NMES [76,78]. Therefore, peripheral muscle adaptations following chronic NMES application likely contribute to improvements in cardiorespiratory fitness.

Thus, NMES has potential to improve both muscle strength and aerobic exercise capacity in older adults. The mechanisms behind adaptations, although poorly understood appear to be similar to those seen following voluntary aerobic exercise and RT. Therefore, NMES could be a viable alternative to voluntary exercise in this population.

7. Challenges to the Use of NMES

Neuromuscular electrical stimulation is used in both clinical and research settings [22], but its implementation into regular clinical practice as an exercise intervention remains difficult. One commonly-reported limiting factor is discomfort felt during electrically evoked contractions [79,80]. Variables such as gender, skin-fold thickness and coping style can influence this perception of discomfort [61]. This issue can be mitigated somewhat by increasing electrode size, therefore dispersing current density [81]. In addition, enhancing user engagement through alternative sensory stimuli, including digital interventions could help to distract from discomfort or from the monotony sometimes associated with exercise [82,83]. Other challenges directly and indirectly associated with discomfort such as engagement with and adherence to technology-assisted exercise regimes over a longer-term can also influence NMES success [84]. Home-based exercise gives the user more flexibility, and user preferences even lean towards unsupervised home-based NMES sessions [85]. Monitoring home-based exercise adherence is important for determining treatment efficacy, treatment dose and whether the patient requires additional support [86,87]. However, monitoring adherence to NMES programmes is difficult and there is a lack of robustly-validated and reliable self-reported adherence measures [88].

8. Supports to use of NMES

Commencing any exercise regime can be a challenging experience for older adults, and many will need additional psychological, social and physical supports to facilitate full participation in the exercise intervention [89–91]. A large body of research is being conducted into techniques designed to support individuals to engage in this kind of behavioural change and overcome the most common barriers to exercise [92–94]. It is evident that there is a requirement for supportive technologies which can both increase user adherence and engagement, and allow therapists to monitor NMES sessions remotely. The following sections will describe techniques which could be combined with an NMES intervention to optimise engagement, adherence, monitoring and ultimately maximise therapeutic outcomes.

8.1. Biofeedback

Biofeedback involves providing an individual with real-time information on select physiological functions with the aim of allowing the individual to influence the physiological parameter based on the feedback [95,96]. A biofeedback system consists of a sensor or measurement tool which detects a particular physiological variable, and an interface where information is presented back to the individual either directly or indirectly, e.g. abstract graphical displays, gamified interfaces or physical components such as robotics [23,97,98], and through visual, audio, haptic or multi-modal outputs [99]. A choice between methods of feedback may improve accessibility for an older adult population where there is an increased prevalence of visual, auditory and other sensory/perceptual impairments [100,101]. In therapy settings, this representation of the measured parameter should be clear, intuitive and designed for the user's needs so that they can easily use the information to alter their performance.

Biofeedback has been shown to promote engagement and adherence to treatments in neurological, orthopaedic and musculoskeletal rehabilitation [23,96,102]. Therefore, by providing real-time information about performance through sensory stimuli specifically designed to correct errors and reinforce positive patterns of behaviour, biofeedback may also facilitate the patient to engage in NMES safely and to a high standard in unsupervised sessions. However, studies to date involving NMES and biofeedback have focused mainly on EMG as part of a targeted-exercise rehabilitation programme [103–105] highlighting a need for future research.

8.2. Gamification

Gamification can be described as the use of game design elements (e.g. points, levels and rewards) in non-game contexts to improve the motivation of users to engage with the system [106,107]. These can influence both intrinsic and extrinsic motivation resulting in a change in health-related behaviour [107–109]. Gamification can be an effective solution to the common problem of decreasing user activity with technology-based interventions [108], and thus could be an ideal technique for improving adherence to an NMES exercise intervention. Studies in older adult populations have used gamification with exercise biofeedback in novel and successful ways, and participants reported the systems to be beneficial, enjoyable and easy to use [110,111]. The current evidence suggests that the addition of gamification elements to a home-based NMES intervention could help to motivate users to engage with the system, while maintaining user activity over time. However, to date no studies have combined gamification with NMES highlighting an interesting gap in the literature.

When developing a gamified interface, it is essential that a user-centred design approach is applied. Engaging with new technologies is a common issue, particularly amongst older adults [84], and therapeutic innovations should employ supportive techniques to address this. Working with older adult users to design, evaluate and implement the system will result in a user-friendly human-computer interface to best support the diverse physical and cognitive needs of an older adult population [112–114]. Other effective digital behaviour-change strategies often effectively paired with gamification or mobile health interventions include motivational messaging, reminder notifications and goal setting [115–117]. These strategies could be promising additions to a technology-based NMES platform.

9. Conclusion

The multi-systemic effects of ageing and its underlying comorbidities and the associated decrease in activity levels can leave older adults both at risk of loss of functional independence, and the inability to participate in the exercise that is necessary to mitigate this risk. NMES appears a feasible and safe alternative to voluntary exercise for the most at-risk older adults, but in its current state suffers from poor clinical acceptability. Challenges to using NMES in a clinical population include discomfort, difficulty engaging and adhering to treatment, and difficulty monitoring remote use. Promising research in other therapeutic fields suggest that incorporating biofeedback and gamification with an NMES treatment could help improve clinical acceptability, highlighting an exciting area for future research. In addition, the use of digital behaviour-change strategies such as reminders and motivational messaging with NMES should also be examined. Future studies should focus on the use of NMES interventions in older adults at a high risk of loss of functional independence, such as those with sarcopenia or multiple co-morbidities.

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