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].

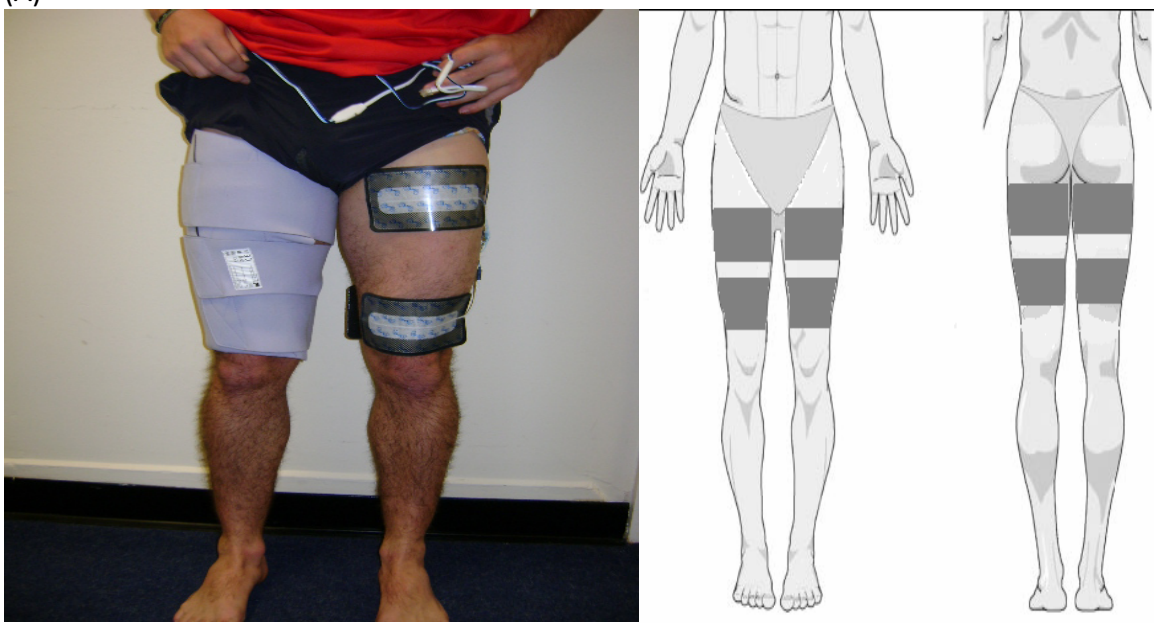
Regular exercise has been shown to delay degenerative processes in senescent muscle [4]. As such, older adults are currently recommended to engage in exercise to prevent morbidity and maintain independence [5]. However, exercise participation is poor in older adults, with those aged 70 - 79 years old 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

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

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

(A)



(B)

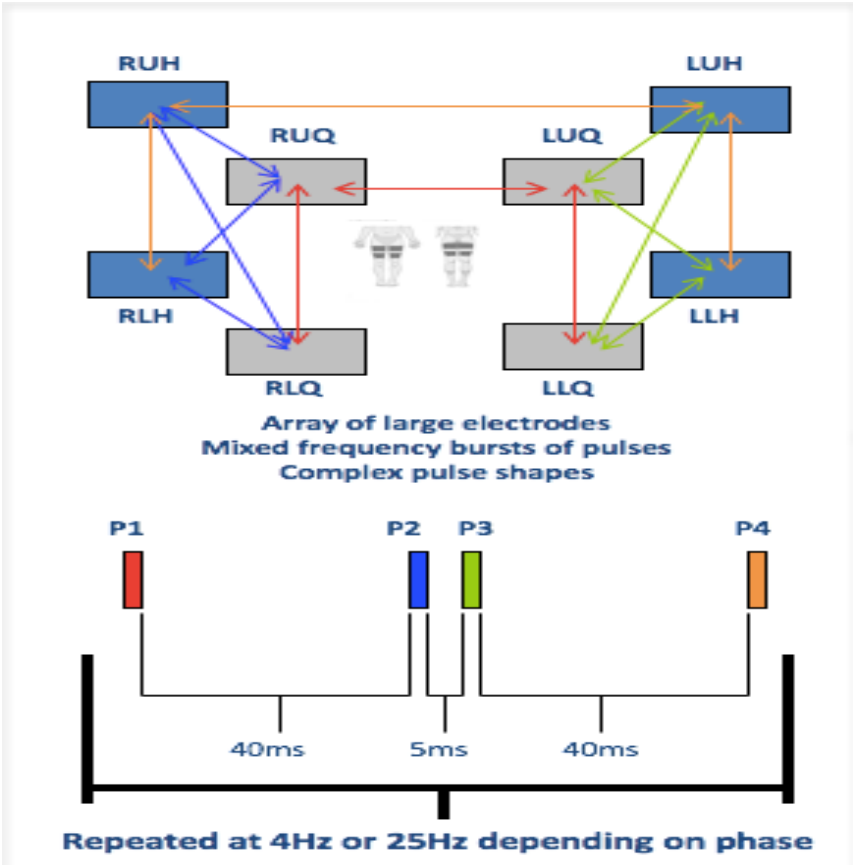


Figure 1. NMES delivery – (A) electrode positions on the quadriceps and hamstrings; (B) multipath delivery system

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].

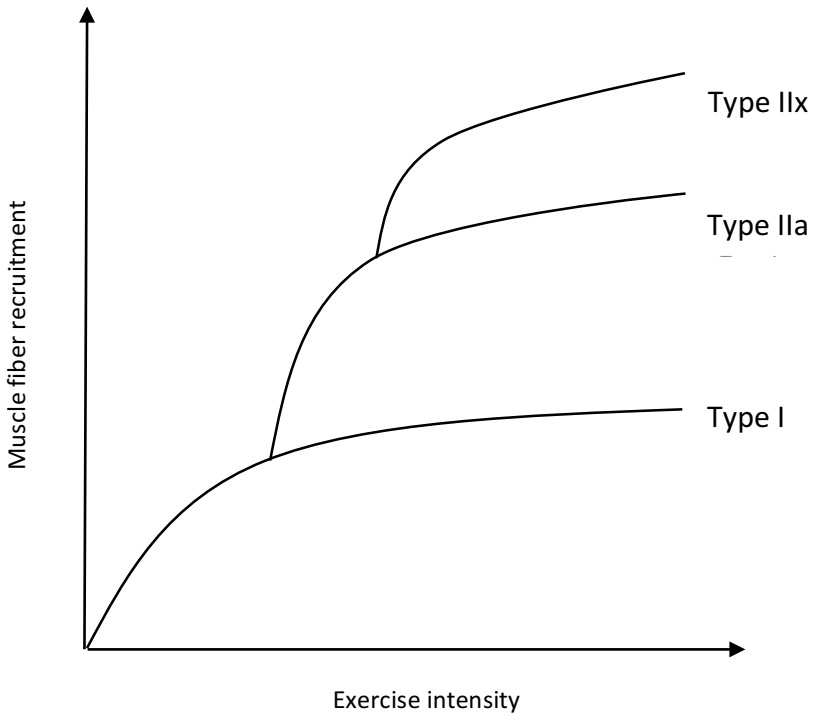


Figure 2. Schematic illustrating the order of muscle fiber recruitment during voluntary exercise.

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-a)) 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].

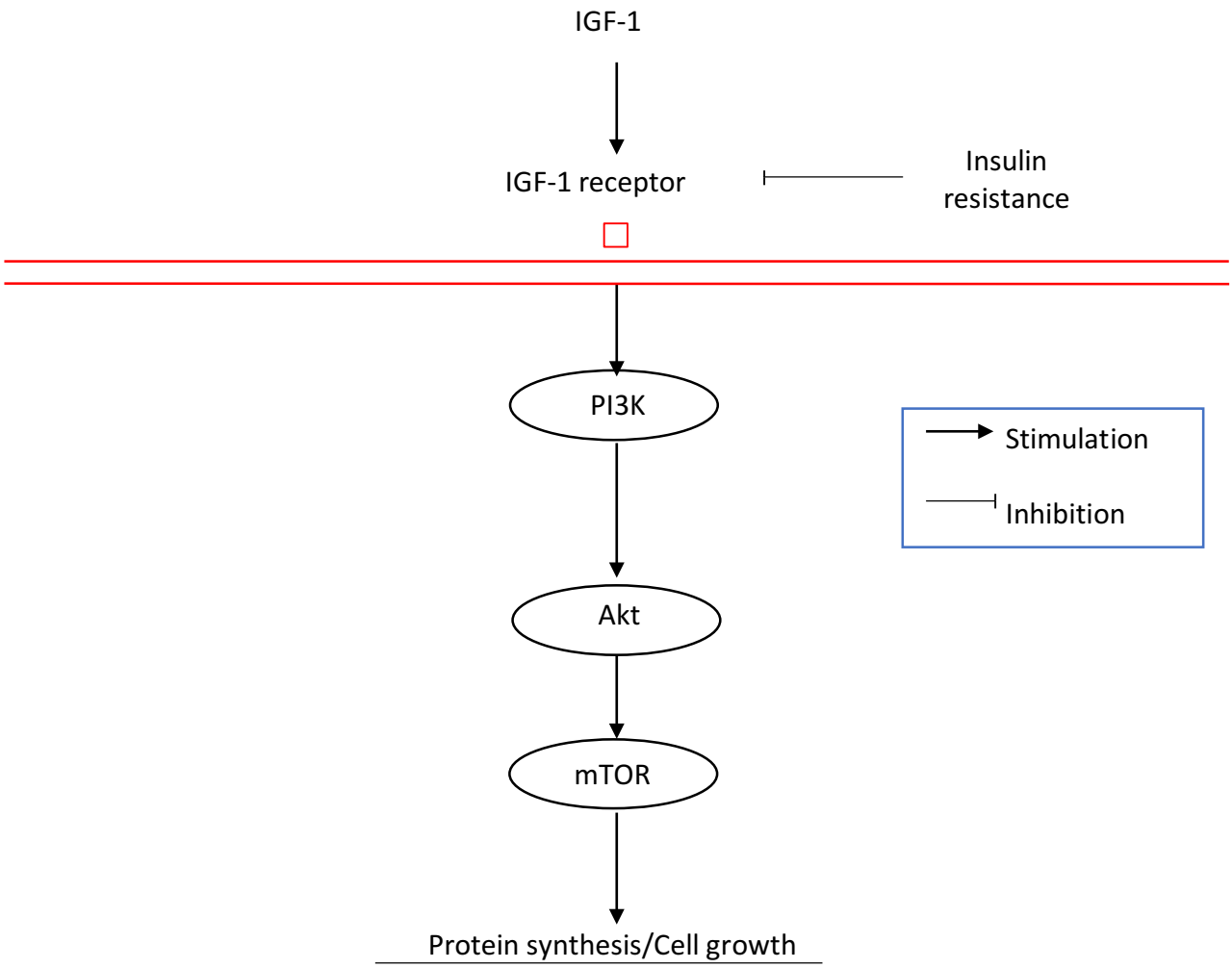


Figure 3. Schematic outlining the IGF-1 signalling pathway. IGF-1, insulin like growth factor-1; PI3K, phosphatidylinositol 3 kinase; Akt/PKB, protein kinase B; mTOR, mammalian target or rapamycin.

241

242 **4. Ageing and the cardiovascular system**

243 Cardiorespiratory fitness, defined as the ability of the cardiovascular and respiratory systems
244 to provide working muscles with oxygen during sustained physical activity is generally
245 expressed as peak oxygen uptake (VO_{2peak}) [41], and is considered an independent predictor of
246 future all-cause mortality in older adults [42]. Cardiorespiratory fitness declines progressively
247 with age and is viewed as a strong predictor of functional capacity [43]. Cross sectional studies
248 have observed typical reductions in VO_{2peak} of 10% per decade [4,44] whilst a maintenance of
249 18-20 $ml.kg.min^{-1}$ is reported as being the minimum value required for activities of daily living
250 [45,46]. Thus, an individual's ability to maintain a sufficient level of aerobic capacity will
251 dictate their functional independence.

252

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

261

262 Thus, physical inactivity contributes to reductions in the neuromuscular and cardiovascular
263 systems both directly and indirectly. Inactivity and physiological changes therefore
264 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

290 [19]. In particular, NMES is seen as an effective intervention in stroke rehabilitation for muscle
291 strengthening and motor recovery [58]. Over three quarters of reported strokes, a leading cause
292 of disability worldwide, occur in over 65's and can impair the pathway between upper and
293 lower motor neurons resulting in impaired muscle activation, reduced activity levels and
294 muscle atrophy [59]. Therefore HF-NMES can target not just the primary effects of ageing but
295 also target the complications of underlying comorbidities.
296
297 Although the use of HF-NMES is more commonly reported in the NMES literature, a growing
298 body of evidence now supports the use of sub-tetanic low frequency NMES (LF-NMES) to
299 induce cardiovascular adaptations and improve exercise tolerance in a variety of populations
300 with frequency ranges typically between 4Hz - 7Hz [11,60,61]. NMES is a safe intervention,
301 with adverse events rarely occurring and evidence of a constant dose response relationship
302 across studies. Furthermore, due to its portability NMES can be applied unsupervised by the
303 user at home. This makes NMES uniquely placed to help attenuate age-related losses of muscle
304 mass, strength and cardiorespiratory fitness.
305
306 **6.1. NMES, strength and muscle mass**
307 Recent systematic reviews have concluded that HF-NMES can be an effective and safe strategy
308 to attenuate the age-related decline in muscle strength [15,16]. Interestingly, reports have
309 concluded that NMES can be as effective as voluntary resistance training for improving
310 strength in older adults [13,15,16]. This has been demonstrated after 8 weeks of HF-NMES
311 (25Hz) in older adults, with a significant 15% increase in isometric quadriceps torque [13],
312 which is similar to improvements reported in voluntary exercise studies [51]. This is of clinical
313 interest given that voluntary exercise can be difficult for this population. In addition, several
314 reports have suggested that the effectiveness of NMES is greatest in the most deconditioned

315 patients [14,16] making HF-NMES a promising intervention to help offset functional
316 impairments associated with ageing in those unable to exercise.
317
318 Although HF- NMES is often referred to as a "peripheral" modality with little influence on the
319 central nervous system (CNS), convincing evidence suggests that both neurological (increased
320 muscle activation) and morphological (increased size and number of Type II fibres) factors
321 dictate strength adaptations [62]. The length of NMES intervention appears to dictate the neural
322 and hypertrophic contribution to strength. Gondin et al [62] investigated the effects of NMES
323 on neural drive and muscle architecture and demonstrated significant improvements in
324 isometric muscle torque (+15%) after 4 weeks of HF-NMES (75Hz) with increased muscle
325 activation (+6%) contributing to improvements in healthy young males. Between week 4 and
326 8 an increase in muscle hypertrophy (+4%) led to further strength gains (+11%) with no
327 significant contribution from increased muscle activation (+1%). In older adults, similar
328 improvements in strength have been reported after 4 weeks of HF-NMES by Caggiano et al
329 [63] (+9%) and Mignardot et al [64] (+26%) respectively, with increased electromyography
330 (EMG) activity suggesting increased muscle activation [64].
331
332 Kern et al. [65] reported significant functional, structural and molecular effects in a group of
333 healthy male and female older adults (73.1 ± 6.9 years) after 9 weeks of HF-NMES (60Hz, 2-
334 3x/week). They reported a 6% increase in maximal isometric torque with a concomitant
335 increase in the size (+2.2%) and percentage (+8%) of Type II fibres [65] suggesting that
336 following an increase in muscle activation, increased Type II fibre hypertrophy may be a
337 primary driver of strength adaptations in older adults. A possible reason for the observed
338 hypertrophy may be due to the non-selective and random muscle recruitment pattern of HF-
339 NMES [66]. This aberrant recruitment highlights a significant benefit of HF-NMES in this

340 population as its use allows for the activation of powerful Type II fibres even at low stimulation
341 intensities [19]. In addition, the authors also reported improved muscle quality. A major
342 contributor to the loss of muscle function is a reduction in muscle quality which is
343 compromised during ageing due to fibrosis and fat accumulation [31]. The authors reported an
344 increase in microRNA-29 [65] (microRNA - small non-coding ribonucleic acids (RNA's)
345 involved in the regulation of gene expression through the degradation or translation
346 suppression of target mRNA's [67]) which is reported to control extracellular matrix (ECM)
347 remodelling in skeletal muscle [68]. Therefore, this increase in microRNA-29 may provide a
348 protective effect potentially counteracting age-related frailty and functional impairments by
349 maintaining muscle quality [65]. This paper by Kern et al [65] demonstrates the most
350 convincing evidence to date of the potential of NMES in this cohort to counteract some of the
351 deleterious effects of ageing.
352
353 At the molecular level a single 60 min HF-NMES session has been shown to increase MPS by
354 27% in senescent muscle [69]. Studies in ICU patients applying NMES for 3-10 days reported
355 similar increases (19.5%) in the phosphorylation of mTOR [70]. Kern et al [65] reported an
356 increase in the expression of IGF-1 and reduced activity of MuRF-1 suggesting that NMES not
357 only regulates anabolic pathways but also modulates muscle catabolism. In addition, NMES
358 may help overcome anabolic resistance in older individuals as even low intensity voluntary
359 contractions may be sufficient to increase the sensitivity of senescent muscle to nutrition
360 [71,72]. Therefore, NMES appears to exhibit positive effects on muscle protein turnover
361 suggesting it may be an effective intervention to help preserve or attenuate age-related
362 reductions in muscle mass.
363
364 **6.2. NMES and cardiorespiratory fitness**

365 Recently the application of LF-NMES protocols (4Hz) which generate rhythmical muscle
366 contractions, similar to shivering, has been shown to increase oxygen demand in various
367 populations [13,60,73,74]. Banerjee et al [73] reported a 10% improvement in VO_{2peak}
368 following 6 weeks of LF-NMES (4Hz, 5x1hr/week) in a middle aged (mean age-48.3 ± 12.0
369 yr) sedentary cohort. Similar improvements have also been reported in patients with chronic
370 heart failure [60]. In healthy older adults, modest improvements in aerobic exercise capacity
371 (+3.5%, 6-min walk distance) have been reported following a 6-week (5x 1hr/week) NMES
372 intervention incorporating a low (4Hz, 45 min continuously) and high frequency (25Hz, 15
373 mins: 5s on/5s off; 15 mins: 5s on/5s off) phase within each 1 hr session [13]. Therefore,
374 repeated application of low frequency NMES over a period of 6-weeks appears to improve
375 exercise tolerance.
376
377 Improvements in cardiorespiratory fitness following voluntary aerobic exercise have been
378 linked to central and peripheral adaptations. The impact of central adaptations on
379 cardiorespiratory fitness improvements following LF-NMES are unclear [75]. However,
380 peripheral adaptations like those observed following voluntary aerobic exercise such as an
381 increase in the content of oxidative enzymes (i.e. citrate synthase) have been reported [76]. In
382 addition, increased phosphorylation of 5'AMP activated protein kinase (AMPK), which
383 regulates cellular metabolism and can control the activity of PPAR gamma co-activator 1 alpha
384 (PGC 1α), the master regulator of mitochondrial biogenesis [77] has been demonstrated after
385 acute and chronic low frequency NMES [76,78]. Therefore, peripheral muscle adaptations
386 following chronic NMES application likely contribute to improvements in cardiorespiratory
387 fitness.
388

389 Thus, NMES has potential to improve both muscle strength and aerobic exercise capacity in
390 older adults. The mechanisms behind adaptations, although poorly understood appear to be
391 similar to those seen following voluntary aerobic exercise and RT. Therefore, NMES could be
392 a viable alternative to voluntary exercise in this population.
393
394 **7. Challenges to the Use of NMES**
395 Neuromuscular electrical stimulation is used in both clinical and research settings [22], but its
396 implementation into regular clinical practice as an exercise intervention remains difficult. One
397 commonly-reported limiting factor is discomfort felt during electrically evoked contractions
398 [79,80]. Variables such as gender, skin-fold thickness and coping style can influence this
399 perception of discomfort [61]. This issue can be mitigated somewhat by increasing electrode
400 size, therefore dispersing current density [81]. In addition, enhancing user engagement through
401 alternative sensory stimuli, including digital interventions could help to distract from
402 discomfort or from the monotony sometimes associated with exercise [82,83]. Other challenges
403 directly and indirectly associated with discomfort such as engagement with and adherence to
404 technology-assisted exercise regimes over a longer-term can also influence NMES success
405 [84]. Home-based exercise gives the user more flexibility, and user preferences even lean
406 towards unsupervised home-based NMES sessions [85]. Monitoring home-based exercise
407 adherence is important for determining treatment efficacy, treatment dose and whether the
408 patient requires additional support [86,87]. However, monitoring adherence to NMES
409 programmes is difficult and there is a lack of robustly-validated and reliable self-reported
410 adherence measures [88].
411
412 **8. Supports to use of NMES**

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

422

423 **8.1. Biofeedback**

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

435

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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