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The effects of neuromuscular electrical stimulation to the ankle pronators on neural excitability & functional status in patients with chronic ankle instability

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ABSTRACT

Objectives: Chronic ankle instability (CAI) is associated with decreased neural excitability that negatively impacts function. This study assessed a 2-week neuromuscular electrical stimulation (NMES) or transcutaneous electrical nerve stimulation (TENS) intervention over the ankle pronators on neural excitability, performance, and patient-reported function in patients with CAI.
Study design: Randomized controlled trial.
Participants: Twenty participants with CAI completed the study.
Main outcome measures: Participants were assessed for reflexive and corticospinal excitability to the ankle muscles, dynamic balance, side-hop test performance and patient-reported outcomes at baseline, post-intervention (2-weeks), and retention (4-weeks). Between baseline and post-intervention, participants reported for 5 sessions where they received either sub-noxious NMES ($n = 11$) or sensory-level TENS ($n = 9$) over the ankle pronators.
Results: Improved reflexive excitability to the ankle pronators was observed in TENS at post-intervention ($p = 0.030$) and retention ($p = 0.029$). Cortical excitability to the dorsiflexors increased in TENS at post-intervention ($p = 0.017$), but not at retention ($p = 0.511$). No significant changes were found for other neural measures, balance ability, hopping, or patient-reported function ($p > 0.050$).
Conclusions: Our results suggest TENS modified neural excitability; however, these changes were not enough to impact clinical function. While TENS may be capable of neuromodulation, it may require rehabilitative exercise to generate lasting changes. NCT04322409.
Level of evidence: Level 2.

1. Introduction

Musculoskeletal injuries, including common ligamentous injuries, present a challenge to clinicians not only due to initial contributions to disablement (e.g. pain, loss of function), but also high rates of re-injury. Recent evidence has suggested that reorganization of the central nervous system is a contributing factor to high rates of joint instability & subsequent re-injury that occurs following anterior cruciate ligament (ACL) tears, ankle sprains, and other ligamentous pathologies (Needle et al., 2017a; Pietrosimone et al., 2022). Theories suggest that acute injury contributes to arthrogenic inhibition in both models of ACL injury and lateral ankle sprains, whereby pain & inflammatory symptoms decrease the ability to activate stabilizing musculature; and chronic symptoms decrease sensory feedback to the central nervous system due to deafferentation & laxity (Kim et al., 2022; Needle et al., 2017a; Pietrosimone et al., 2022). Thus, the central nervous system reorganizes in such a way that an increased amount of cortical resources are recruited to overcome decreased motor activation in

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simple, stereotyped movements (Grooms et al., 2016). As clinical assessments typically require simple movement (e.g. hopping), patients can potentially appear recovered using these atypical cortical pathways. However, when returning to unconstrained activity that may require a greater attentional demand, the loss of movement planning efficiency leads to deleterious muscle activation strategies and subsequently reinjury (Burcal et al., 2019).

This pattern of maladaptive neuroplasticity has largely been observed in patients with ACL injury and those with ankle sprains & chronic ankle instability (CAI) (Needle et al., 2017a). While considered less severe than ACL injury, ankle sprains are the most common injury observed in physically active individuals and contribute to several negative long-term sequelae, including repeated rolling & CAI, post-traumatic ankle osteoarthritis, and long-term decrements in physical activity and health-related quality of life (Herzog et al., 2019; Houston et al., 2015; Hubbard-Turner & Turner, 2015; Wikstrom et al., 2019). While similarities exist between ACL injuries & ankle sprains including the presence of maladaptive neuroplasticity, there are some important differences in these models such as injury severity (rupture vs. partial tears), surgical management, and stabilizing musculature. Consequently, interventions should be assessed in each model to determine relative efficacy.

As maladaptive neuroplasticity is an underlying factor for high re-injury rates (Grooms et al., 2022; Needle et al., 2017a), encouraging proper activation of muscle through disinhibition of motor areas should be a priority in the clinical setting. A frequently used intervention for achieving this among patients with ACL injury is the use of neuromuscular electrical stimulation (NMES) to increase activation of the quadriceps femoris muscles (Imoto et al., 2011; Lake, 1992; Lepley et al., 2015). It is hypothesized that high levels of sensory feedback associated with strong muscle contraction contributes to disinhibition within the primary motor cortex, thus improving function among these individuals (Lepley et al., 2015). While NMES is commonly used in clinical practice following ACL injury, the clinical use of NMES to treat CAI is less common, with research studies focusing on the role of these interventions on acute ankle sprain (Yoshida et al., 2015). Given the similarities in the motor inhibition that occurs through these two ligamentous injuries (Needle et al., 2017a), one could posit that similar stimulation to the peroneus longus – the primary stabilizer against the common supination mechanism of lateral ankle sprains – may have similar effects on neurological & muscle activation, subsequently yielding improvements in muscle function and patient-reported function (Bruce et al., 2020).

The purpose of this study was to assess the use of NMES, compared to a comparator treatment of sensory-level transcutaneous electrical nerve stimulation (TENS), on neural excitability to the ankle, performance, and patient-reported function in patients with CAI. We hypothesized that due to the increased sensory feedback of muscle contraction associated with NMES, neural excitability would increase, and therefore facilitate improvements in dynamic postural control, functional performance, and patient-reported function.

2. Methods

2.1. Study Design

This study implemented a longitudinal, parallel, randomized controlled trial to explore the efficacy of NMES, compared to sensory-level TENS on improving neural excitability & function in individuals with CAI. Participants were assessed at three time-points (Baseline; 2-weeks: Post-Intervention; 4-weeks: Retention), and were treated 5 times with electrical stimulation between the baseline & post-intervention time-points. Independent variables included group (NMES vs. TENS) and time (Baseline, Post-intervention, Retention). Dependent variables included reflexive & cortical excitability to the peroneus longus (PL), tibialis anterior (TA), and soleus (SOL), intracortical inhibition, dynamic balance & muscle activation, isometric strength, functional performance, and patient-reported outcomes of ankle & global disablement. Participants & assessors were both blinded to group assignment for the first 11 subjects; however, due to the COVID-19 pandemic, personnel changes forced removal of the assessor blind for the final 9 subjects.

2.2. Participants

Twenty individuals with CAI between the ages of 18 and 35 were recruited for this investigation. Patients were classified as having CAI if they reported at least one ankle sprain more than a year prior to study enrollment, experienced recurrent sensations of ankle rolling during activity, and scored greater than a 10 on the Identification of Functional Ankle Instability instrument (IdFAI). If participants had bilateral instability, the leg with the higher IdFAI score was selected. Subjects were recruited from a University setting through flyers, class announcements, and website postings. Subjects were excluded if they had an injury that limited physical activity within the 3 months prior to the study, or had a history of fracture or surgery to the lower leg. Participants also met criteria for the safe practice of transcranial magnetic stimulation (TMS) (Groppa et al., 2012). All participants provided institution-approved informed consent (20−0042) and the study was registered on ClinicalTrials.gov (NCT04322409). Following the baseline session, participants were randomly allocated to the experimental NMES group, or control TENS group using a block randomization scheme with blocks sizes of 4−6. The randomization scheme accounted for 24 potential participants to account for potential dropouts.

Sample size was based on preliminary data and previously published data in the ACL model, given similarities in physiologic adaptations in these patients (Lepley et al., 2015). Based on dependent variables of cortical excitability and patient-reported function, we estimated an effect size (d) of 0.99−1.25. With power (1-β) set at 0.8 and an a priori level of significance (α) of 0.05, we determined 10 subjects per group would be sufficient to achieve statistical significance.

2.3. Assessment of dependent variables

2.3.1. Neural excitability

Measures of reflexive & cortical excitability were assessed in a Faraday-shielded electrophysiology laboratory. Participants were instrumented with electromyography (EMG) electrodes (EMG analyzer, B&L Engineering, Santa Ana, CA) over the PL, TA, and SOL muscles by palpating, shaving, cleaning with 70% ethanol, and abrading the areas over the muscle, prior to securing electrodes with an elastic wrap (Delagi et al., 2011). Reflexive excitability was assessed with the subject prone, through electrical stimulation of the sciatic nerve prior to its bifurcation in the popliteal fossa. 1 ms square pulses were applied using a bar electrode connected to a constant current stimulator (DS7R, Digitimer, Hertfordshire, UK) to locate the nerve by observing the location that gave the largest contraction across all muscles at the lowest intensity (Bruce et al., 2020; Hoffman et al., 2003). Then the stimulator output was reduced to 0, and square pulses were applied every 10s with the stimulator output increasing by 1 mA each pulse with one pulse per intensity, until a maximal response was observed across all three muscles. EMG data were collected at 2000 Hz using custom LabVIEW software (National Instruments, Austin, TX). Data were

processed offline with separate custom LabVIEW software. Peak-to-peak EMG amplitude was extracted 10–30 ms (M-wave) and 30–60 ms (H-wave) following the stimulus. The ratio of the maximum M-wave (M_{max}) to maximum H-wave (H_{max}) was extracted for each muscle.

Cortical excitability & intracortical inhibition were assessed using TMS with the patient seated in a motorized chair. A double-conical coil was connected to a 2.0T magnetic stimulator (200-2, Magstim LTD, Wales, UK) and was placed 1 cm anterior and lateral to the participant-identified vertex of the skull to provide magnetic stimuli to the cortical representation of the lower leg muscles. Subjects were familiarized with the stimulator as gradually increasing pulses were applied until a motor response was visible in the leg. The lower extremity hotspot was then identified by searching approximately a 5 cm^2 (Needle et al., 2017a) area centered anterior and lateral to the vertex of the skull as responses from the lower leg muscles were monitored in custom LabVIEW software. Given the proximity of the lower leg muscle representation within the primary motor cortex, and the greater cortical excitability of the TA, responses from the TA were used to mark the hotspot (Needle et al., 2013; Wassermann et al., 1992). Once the hotspot was identified, a stimulus-response curve was obtained by applying 40 to 50 pulses 4–7s apart with intensities ranging from sub-threshold to supra-maximal while the subject remained relaxed (Peri et al., 2017). The curve obtained was used to identify the resting motor threshold (RMT) of the PL (Needle et al., 2013). Participants were then asked to maintain a contraction in the direction of ankle pronation of approximately 15–20% of maximal effort with investigator feedback as 10 pulses were applied each at 110%, and 130% RMT. All stimuli were triggered and time-synchronized with EMG data in custom LabVIEW software at 2000 Hz.

The stimulus-response curve was fitted with a Levenberg-Marquardt algorithm to a modified Boltzmann equation to obtain outcome measures of maximum motor evoked potential (MEP_{max}), and derive the RMT for all muscles (Devanne et al., 1997; Peri et al., 2017). Lastly, intracortical inhibition was determined through the cortical silent period (CSP) (Kimberley et al., 2009; Nilsson et al., 1997; Stirling et al., 2018). These techniques are associated with good to excellent reliability (Hoffman et al., 2003; Kimberley et al., 2009; Peri et al., 2017).

2.3.2. Performance measures

Dynamic postural stability was assessed in a biomechanics laboratory. Maximal jump height was assessed on a Vertec jump trainer (Sports Imports, Hilliard, OH). Participants then stood 70 cm from the edge of an in-ground force plate (Bertec FP6090-15) and hopped forward and to a vertical height of 50% of their maximum jump, stabilize as quickly as possible, and maintain that stance for 15s. Participants were allowed to practice the jump until they felt comfortable, and then performed 5 successful trials (i.e. jumped to adequate height, landed on force plate, maintained unipedal stance throughout landing). Force data was collected in LabVIEW software at 1000 Hz. Stability indices were calculated in anteroposterior (APSI), mediolateral (MLSI), and vertical (VSI) planes, as well as a composite dynamic postural stability index (DPSI) as described by Wikstrom et al. (Wikstrom et al., 2007). The DPSI is associated with excellent precision (SEM = 0.03) and intersession reliability (ICC = 0.96). (Wikstrom et al., 2005).

Functional performance was assessed using a single-leg side-hop test (Rosen et al., 2019). Participants were asked to hop laterally over two lines oriented in the anteroposterior plane, placed 30 cm apart. Participants were provided a practice trial, rest period, and then were instructed to hop back and forth over the 2 lines a total of 20 times (10 each direction). Time to perform was extracted as test performance, and has demonstrated good inter-session reliability (ICC = 0.80) and precision (SEM = 2.10) (Caffrey et al., 2009). Ankle pronator strength was assessed using a handheld dynamometer (Lafayette Instrument, Lafayette, IN) (Mentiplay et al., 2015). Participants laid on the non-test side, with the non-test hip flexed forward. The test side was stabilized against the table, while the dynamometer was placed on the lateral aspect of the 5th metatarsal. Participants were instructed to pronate against resistance, with verbal encouragement, for a total of 3 trials. The same investigator tested each subject's strength and the average of the 3 trials was used for analysis to achieve moderate reliability (Mentiplay et al., 2015).

Patient-reported outcomes in this investigation included the Foot & Ankle Ability Measure activity of daily living (FAAM-ADL) and sport (FAAM-sport) subscales (Martin et al., 2005), the 11-item Tampa Scale for Kinesiophobia (TSK) (Woby et al., 2005), and the modified Disablement in the Physically Active Scale (DPA) (Vela & Denegar, 2010). Questionnaires were collected and managed using REDCap (Research Electronic Data Capture) tools hosted within the investigator's institution (Harris et al., 2009).

2.4. Intervention

All participants reported for 5 intervention sessions over the 2 weeks between baseline and post-intervention testing to receive an electrical stimulation treatment lasting 11 min. Intervention sessions were separated between 2 and 4 days. Upon reporting to the laboratory, two 2" cloth electrical stimulation electrodes (Valutrode, Axelgaard, Fallbrook, CA) were placed over the superior and inferior portions of the peroneus longus muscle, and connected to an electrical stimulator (Chattanooga Vectra Genisys, DJO Global, Lewisville, TX). Participants in the NMES group received 11 min of a biphasic current with a 10:50 duty cycle, 2s ramp time, 75 Hz burst frequency, and 250 μsec phase duration (allowing for 10 full cycles). Intensity was turned up to a sub-noxious threshold, where participants were asked to tolerate as strong a contraction as possible without pain (Conley et al., 2021; Lepley et al., 2015). Participants in the TENS group received a biphasic current at a frequency of 100 Hz and phase duration of 100 μsec for 11 min to match the treatment duration of the NMES group (Starkey, 2013). Intensity was turned above the sensory threshold, but with no visible motor contraction. TENS was selected as a comparator treatment to standardize the treatment timing, participant perception, and electrode placement that would allow for determining specific effects of NMES, with data indicating a minimal effect on individuals following ligament injury (Hart et al., 2012). Both groups were continuously monitored for intensity, with the NMES group asked each cycle if they could tolerate a stronger contraction, and participants in the TENS group ensuring they still felt the sensory stimulation.

2.5. Data analysis

Data were assessed using factorial analysis of variance, with the between-subjects factor of group (NMES, TENS) and within-subjects factor of time (Baseline, Post-Intervention, Retention). For measures of neural excitability, muscle (TA, PL, SOL) was added as an additional within-subjects factor. For assessment of cortical silent period, intensity (110 or 130 percent of RMT) was added as an additional within-subjects factor. Post hoc testing was performed using Fisher's LSD. Effect sizes were assessed through partial eta squared (η^2) with 0.01 considered a small effect, 0.06 considered a medium effect, and 0.14 considered a large effect (Cohen, 1992). An a priori level of significance was set at 0.05.

3. Results

3.1. Participants

A total of 20 participants completed the protocol. Participant characteristics are presented in Table 1, and the flow of participants through the study are presented in Fig. 1. No significant differences were observed between groups for sex, age, height, mass, or IdFAI scores (Table 1).

3.2. Neural excitability

Means and standard deviations for neural excitability variables are presented in Table 2. For reflexive excitability (H_{max}:M_{max}), a significant group-by-time-by-muscle interaction effect was observed ($F_{4,68} = 3.007$, $P = 0.024$, $\eta^2 = 0.150$). Pairwise comparisons showed no changes in the TA between groups or across time points. Reflexive excitability to the PL was equal across groups at baseline ($p = 0.650$), but was greater in the TENS group at post-intervention ($p = 0.030$) and retention ($p = 0.029$). Reflexive excitability to the soleus decreased in the TENS group at post-intervention ($p = 0.006$), but was not significantly different from baseline at retention ($p = 0.293$).

Analysis of RMT revealed a significant group-by-time-by-muscle interaction effect ($F_{2,30} = 3.741$, $p = 0.035$, $\eta^2 = 0.200$). Pairwise comparisons revealed no changes within the NMES group over time; however, a significant decrease in RMT to the TA, indicating greater excitability, was observed in the TENS group from baseline to post-intervention ($P = 0.017$); however, there was no difference from baseline at retention ($P = 0.511$). For the PL, RMT did not change from baseline to post-intervention ($p = 0.615$); however, a significant increase in RMT (decreased excitability) was observed between post-intervention & retention ($p = 0.030$) in the TENS group. Maximum MEP did not reveal a significant group-by-time-by-muscle interaction effect ($F_{2,30} = 0.143$, $p = 0.867$, $\eta^2 = 0.009$), nor were other interaction effects significant. There was no main effect of time ($F_{2,30} = 1.127$, $p = 0.337$, $\eta^2 = 0.07$). Only a significant main effect of muscle was observed ($F_{1,15} = 13.634$, $p = 0.002$, $\eta^2 = 0.476$), indicating greater excitability to the TA than the PL.

No significant group-by-time-by-intensity interaction effect was observed for the cortical silent period ($F_{2,36} = 0.795$, $p = 0.459$, $\eta^2 = 0.042$). Only a significant main effect of Intensity was observed ($F_{1,18} = 23.692$, $p < 0.001$, $\eta^2 = 0.568$), reflecting a longer CSP at 130% RMT than 110% RMT. There was no significant main effect of time ($F_{2,36} = 1.956$, $p = 0.156$, $\eta^2 = 0.098$).

3.3. Functional measures

Means and standard deviations for functional variables including performance & patient-reported function are presented in Table 3. No significant group-by-time effects were observed for DPSI ($F_{2,36} = 0.079$, $P = 0.924$, $\eta^2 = 0.004$), and no time-by-group-by-direction effect was observed for other postural stability indices ($F_{2,36} = 1.289$, $P = 0.282$, $\eta^2 = 0.067$). No other interaction effects were observed, nor were main effects of group or time observed. The side hop test showed no significant group-by-time interaction effect ($F_{2,36} = 0.142$, $P = 0.868$, $\eta^2 = 0.008$), nor were significant main effects of time ($F_{2,36} = 1.239$, $P = 0.302$, $\eta^2 = 0.064$) or group ($F_{1,18} = 0.031$, $P = 0.862$, $\eta^2 = 0.002$) observed. Strength showed no significant group-by-time interaction effect ($F_{2,36} = 1.915$, $P = 0.162$, $\eta^2 = 0.096$), nor were significant main effects of time ($F_{2,36} = 0.395$, $P = 0.677$, $\eta^2 = 0.021$) or group ($F_{1,18} = 0.010$, $P = 0.920$, $\eta^2 = 0.001$) observed.

Patient-reported outcome measures followed similar trends. The FAAM-ADL showed no significant group-by-time interaction effect ($F_{2,32} = 0.500$, $P = 0.611$, $\eta^2 = 0.030$), nor were significant main effects of time ($F_{2,32} = 0.085$, $P = 0.919$, $\eta^2 = 0.005$) or group ($F_{1,16} = 0.043$, $P = 0.838$, $\eta^2 = 0.003$) observed. The FAAM-Sport showed no significant group-by-time interaction effect ($F_{2,32} = 1.456$, $P = 0.248$, $\eta^2 = 0.083$), nor were significant main effects of time ($F_{2,32} = 0.295$, $P = 0.746$, $\eta^2 = 0.018$) or group ($F_{1,16} = 0.177$, $P = 0.680$, $\eta^2 = 0.011$) observed. TSK scores displayed no significant group-by-time interaction effect ($F_{2,30} = 0.273$, $P = 0.763$, $\eta^2 = 0.018$), nor were significant main effects of time ($F_{2,30} = 2.435$, $P = 0.105$, $\eta^2 = 0.140$) or group ($F_{1,15} = 0.129$, $P = 0.725$, $\eta^2 = 0.009$) observed. Lastly, mDPA scores showed no significant group-by-time interaction effect ($F_{2,30} = 2.045$, $P = 0.147$, $\eta^2 = 0.120$), nor were significant main effects of time ($F_{2,30} = 1.688$, $P = 0.202$, $\eta^2 = 0.101$) or group ($F_{1,15} = 0.057$, $P = 0.814$, $\eta^2 = 0.004$) observed.

Table 1
Means (standard deviation) of subject demographics. *IdFAI*, Identification of Functional Ankle Instability questionnaire; *NMES*, neuromuscular electrical stimulation group; *TENS*, transcutaneous electrical stimulation group.

	NMES	TENS	t (p)[a]
N (M/F)	11 (4/7)	9 (4/5)	0.135[b] (0.714)
Age (yrs)	23.6 (4.7)	21.9 (4.1)	0.875 (0.393)
Height (cm)	169.3 (13.1)	172.6 (10.1)	0.606 (0.552)
Mass (kg)	74.5 (17.5)	73.0 (18.7)	0.719 (0.848)
IdFAI score	17.36 (1.96)	18.37 (4.42)	0.681 (0.511)

[a] Values in column are from Student's t-tests.
[b] Chi-squared value as data were categorical.

4. Discussion

This study aimed to assess the efficacy of NMES compared to sensory TENS on affecting neural excitability & function among individuals with CAI. Our results suggest that, contrary to our hypothesis, TENS offered some benefits to neural excitability beyond NMES; however, these changes were not sufficient to impact functional performance.

4.1. Neural excitability

The finding that TENS improves neural excitability is not particularly novel; however, there has been limited exploration in lower extremity and injury models, as well as interventions beyond a single session. Previous research has demonstrated improvements in neural excitability following the acute use of TENS, believed to be generated by disinhibitory effects of increased afferent fiber activation (Hardy et al., 2002; Jadidi et al., 2022; Tinazzi et al., 2006). While this yields increased cortical excitability following TENS interventions, many of our findings were noted reflexively in the form of increased H_{max}:M_{max} ratios to the ankle pronators and a decreased responses from the soleus. The facilitation of ankle pronator excitability in contrast to the decrease in plantarflexor excitability is likely due to electrode placement, with electrodes placed over the pronators on the lateral aspect of the shank. The reflexive properties of the soleus are typically greater than that of the PL, reflecting the muscle's function in regulating posture (Hoffman et al., 2003). Therefore, afferent stimulation from TENS may have raised excitability to a phasic muscle (PL), while decreasing excitability to the postural soleus. Our results did also note a change in corticospinal excitability in the TENS group as well, with dorsiflexor excitability rising post-intervention, but not at retention. This is a notably desirable change among patients with CAI, as the dorsiflexors are a key stabilizer of the ankle joint; however, it is unclear why only this muscle improved excitability

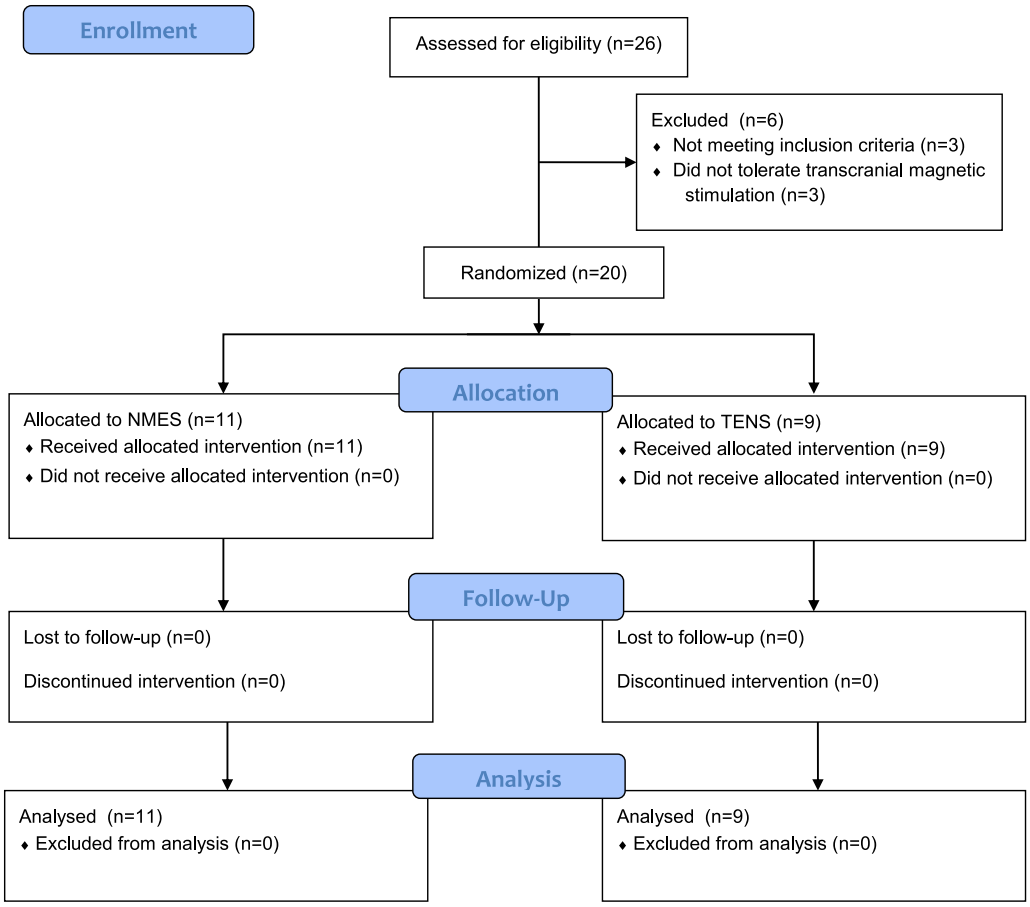

Fig. 1. Consort 2010 Flow Diagram of participant enrollment, allocation, follow-up, and analysis.

Table 2
Means (standard deviation) of neurological variables. *RMT,* Resting motor threshold; *MEPmax,* Maximum motor evoked potential; *CSP,* cortical silent period; *NMES,* neuromuscular electrical stimulation group; *TENS,* transcutaneous electrical stimulation group.

Variable	Muscle	NMES			TENS			Time-by-Group-by-Muscle effect[a]	
		Baseline	Post-Intervention	Retention	Baseline	Post-Intervention	Retention	F	p
H_{max}:M_{max} ratio	TA	0.178 (0.080)	0.155 (0.106)	0.148 (0.101)	0.190 (0.101)	0.136 (0.048)	0.201 (0.122)	3.007	0.024
	PL	0.213 (0.129)	0.166 (0.088)	0.150 (0.110)	0.245 (0.147)	0.276[b] (0.115)	0.292[b] (0.152)		
	SOL	0.512 (0.161)	0.506 (0.201)	0.476 (0.227)	0.663[b] (0.097)	0.493[c] (0.214)	0.606 (0.202)		
RMT (%2T)	TA	35.41 (8.63)	32.18 (12.47)	34.50 (11.50)	38.60 (15.36)	29.98[c] (11.64)	35.63 (12.22)	3.741	0.035
	PL	38.24 (9.39)	34.42 (11.23)	33.83 (11.73)	32.87 (12.35)	31.17 (14.42)	39.95[d] (13.40)		
MEP_{max} (%M_{max})	TA	0.15 (0.10)	0.15 (0.13)	0.16 (0.11)	0.26 (0.19)	0.19 (0.13)	0.23 (0.24)	0.143	0.867
	PL	0.08 (0.08)	0.08 (0.04)	0.08 (0.04)	0.13 (0.14)	0.08 (0.06)	0.09 (0.04)		
CSP 110% (ms)	PL	233.5 (87.7)	237.7 (117.9)	245.8 (85.8)	241.0 (75.6)	205.7 (29.5)	209.6 (71.2)	0.795	0.459
CSP 130% (ms)	PL	332.6 (107.1)	279.27 (114.2)	330.6 (85.3)	297.2 (107.0)	243.4 (59.2)	238.1 (72.2)		

[a].Column represents results of factorial analysis of variance.
[b] Difference between groups ($P < 0.05$).
[c] Difference from baseline ($P < 0.05$).
[d] Difference from post-intervention ($P < 0.05$).

given that the TA was not targeted by this intervention. One potential explanation is that the TA has higher cortical representation than the other lower leg muscles (Needle et al., 2013), therefore making it an easier muscle in which to detect corticospinal changes. The focus of previous research has been on the effects of TENS on neural excitability to the upper extremity over single sessions (Hardy et al., 2002; Jadidi et al., 2022; Tinazzi et al., 2006); however, the lower extremity offers differences as cortical representation for the foot & ankle are notably less than the wrist & hand muscles, with the latter offering a better opportunity to observe differences. Similarly, the repeated bouts of stimulation over two weeks may have served to generate further differences than those single, acute intervention designs. Therefore, we may conclude effects of 5 doses of TENS over 2 weeks may generate lasting effects only at the segmental level.

Contrary to our hypotheses and previous research (Conley et al., 2021; Kim et al., 2010; Lepley et al., 2015), NMES did not yield an increase in cortical or reflexive excitability. In this study, NMES

Table 3
Means (standard deviation) of performance & patient-reported function variables. *DPSI,* dynamic postural stability index; *APSI,* anteroposterior stability index, *MLSI,* mediolateral stability index, *VSI,* vertical stability index; *SHT,* side-hop test; *FAAM-ADL,* Foot & Ankle Ability Measure Activities of Daily Living subscale; *FAAM-Sport,* Foot & Ankle Ability Measure Sport subscale; *DPAS,* Disablement in the Physically Active Scale; *TSK-11,* Tampa Scale for Kinesiophobia; *NMES,* neuromuscular electrical stimulation group; *TENS,* transcutaneous electrical stimulation group.

	NMES			TENS			Time-by-Group Effect[a]	
	Baseline	Post-Intervention	Retention	Baseline	Post-Intervention	Retention	F	*p*
DPSI	0.508 (0.056)	0.505 (0.046)	0.507 (0.056)	0.488 (0.042)	0.486 (0.047)	0.494 (0.045)	0.079	0.924
APSI	0.126 (0.011)	0.135 (0.014)	0.128 (0.015)	0.141 (0.016)	0.129 (0.014)	0.128 (0.015)	0.055	0.947
MLSI	0.045 (0.016)	0.039 (0.011)	0.039 (0.012)	0.036 (0.007)	0.037 (0.005)	0.035 (0.006)		
VSI	0.490 (0.059)	0.484 (0.048)	0.488 (0.059)	0.465 (0.042)	0.466 (0.051)	0.488 (0.059)		
SHT (s)	14.1 (6.1)	13.6 (10.3)	12.6 (6.7)	13.8 (5.1)	12.5 (3.4)	23.4 (4.6)	0.142	0.868
Strength (lbs)	50.2 (5.1)	47.5 (7.4)	47.8 (9.6)	46.5 (9.9)	48.6 (12.2)	51.4 (9.0)	1.915	0.162
FAAM-ADL	97.1 (2.1)	97.4 (2.9)	96.5 (4.5)	96.9 (5.6)	95.9 (8.1)	96.9 (5.7)	0.500	0.611
FAAM-Sport	91.4 (7.0)	92.9 (9.4)	92.9 (9.1)	92.9 (9.2)	88.8 (13.1)	89.7 (14.3)	1.456	0.248
DPAS	9.6 (4.9)	5.6 (6.8)	5.4 (7.7)	6.0 (6.5)	6.4 (7.5)	6.0 (7.3)	2.045	0.147
TSK-11	31.1 (8.1)	32.8 (6.6)	31.5 (7.1)	29.1 (5.8)	32.6 (4.7)	30.6 (4.7)	0.273	0.763

[a] Column represents results of factorial analysis of variance.

parameters were selected to provide sub-noxious, high-intensity motor stimulation over a series of ten 10-s bursts. While parameters of NMES and targeted neural effects vary across published research, we selected this intervention to generate cortical disinhibition by activating larger motor units and using high threshold stimulation to reverse inhibitory changes that may be limiting muscle activation (Lepley et al., 2015). To our knowledge, no studies have directly compared the use of TENS and NMES on neural excitability. Given that TENS is primarily used to treat pain-related conditions and NMES is primarily used in conditions where muscle activation is limited – both with strong clinical effects – we expected NMES to yield more potent changes to neural excitability (Harkey et al., 2014). We may have observed these limited effects because outcome measures were assessed more than 24 h from their final intervention. Alternately, Lepley et al. (Lepley et al., 2015) has highlighted the importance of increasing the simulation intensity to the maximum tolerable level as stimulators with higher maximum output yield stronger effect sizes (Conley et al., 2021; Kim et al., 2010); however, there may be device and or/participant-specific limitations on the ability to reach a high enough intensity in order to generate disinhibitory effects. While we encouraged participants to endure higher intensities, we still aimed to maintain sub-noxious levels. Future studies may aim to compare NMES at various intensity thresholds to better understand the relationship between stimulation dosage and neural excitability.

When considering injury status, much of the basis for the current research rests in studies related to ACL ligament tears combined with the similarities in neural adaptations between that population and patients with CAI. While not specifically investigating neural excitability, we utilized TENS as a control treatment based on findings from Hart et al. (Hart et al., 2012) that indicated no effects of TENS on quadriceps function following ACL injury. Meanwhile, NMES has been described as a moderately effective intervention for improving quadriceps function and neural excitability following ACL injury, albeit dependent on stimulation parameters (Conley et al., 2021; Lepley et al., 2015). This highlights a notable discrepancy when considering ACL & ankle injury models. Although the injuries present with similar patterns of maladaptive neuroplasticity-related changes, they appear to have differential responses to interventions. Much of this may lie in physiologic differences between the ankle & knee stabilizers. The quadriceps are a large, high force-producing muscle group designed to function primarily in the sagittal plane, while the ankle pronators are a notably smaller muscle group consisting of pennate muscles that have a large reliance on co-contraction to maintain ankle joint stability, particularly in the frontal plane (Needle et al., 2017b).

Further, the timing of the injury relative to the intervention is of note, as many individuals experienced their initial ankle sprain years before seeking treatment for CAI, whereas ACL injuries are typically treated from the time of injury and/or surgery, advancing the ability of individuals to better address symptoms. Similarly, CAI may represent a more chronic maladaptive state similar to osteoarthritis (OA). TENS has been shown to be an effective disinhibitory intervention, increasing quadriceps central activation ratio among individuals with knee OA (Pietrosimone et al., 2009, 2011). Also, similar to the current study, despite activation changes, Pietrosimone et al. (Pietrosimone et al., 2011) did not observe statistically significant changes in patient-reported outcome measures among OA patients participating in a 4-week TENS and exercise intervention. These results demonstrate that changes in patient-perceived function may trail changes in neural measures and that longer monitoring of functional changes may be necessary in future investigations.

4.2. Functional outcomes

In considering the implementation of TENS or NMES in patients with CAI, potential effects go beyond neural excitability. In fact, the use of NMES following ACL injury is much better supported using functional outcomes (e.g. strength, hop performance) over neural measures. However, our results did not indicate improvements in strength, balance, muscle activation, or patient-reported function through either intervention. While these data are contrary to investigations utilizing patients with ACL injury, a notable difference in the current investigations was the use of isolated electrical stimulation paradigms. Subjects were not enrolled in ankle rehabilitation programs, nor did they do exercises concurrently as part of this investigation. While electrical stimulation is described to enhance function in patients with ACL injury, this is typically combined with exercise-based interventions. Further, as noted earlier, in more chronic joint models such as OA, changes in patient-reported outcome measures may trail improvements in neural function (Pietrosimone et al., 2011).

Previous data in patients with CAI suggest that disinhibitory interventions that yield improvements in neural excitability leads to improved patient-reported outcomes & functional ability, contrary to our data (Bruce et al., 2020). Given that TENS did display disinhibitory effects towards reflexive excitability, reason would suggest function should have improved to some point. This discrepancy may highlight the importance of restoring cortical

excitability among these patients as the intervention in that investigation (transcranial direct current stimulation) served to improve cortical excitability, whereas these peripheral electrical stimulation-based interventions did not. Further this study combined the disinhibitory intervention with strengthening activities that emphasizes the potential importance of combining these interventions with rehabilitative exercise.

4.3. Limitations

While our data suggest TENS and NMES in isolation may not be effective in improving outcomes in patients with CAI over a two week intervention, we do urge caution in this interpretation. In this study, we performed an isolated electrical stimulation intervention in the absence of rehabilitative exercise, which does not reflect what would be performed in a clinical setting. However, the isolation of this intervention allows for its effects to be better determined and we would encourage subsequent investigations that pair electrical stimulation paradigms with exercise in this population.

5. Conclusions

The results of this study suggest that neither TENS nor NMES used in isolation are effective for improving clinical outcomes in patients with CAI; however, TENS may be beneficial for improving reflexive excitability. This presents notable discrepancies from models that utilize NMES in the treatment of ACL injury and highlights important differences between these populations that share similar maladaptive neural changes. There are currently large discrepancies in the parameters and treatment frequency utilized in clinical and research settings with regard to TENS & NMES interventions, likely contributing to varied outcomes (Conley et al., 2021). Future investigations should attempt to resolve dosage discrepancies as well as distinguish the isolated versus combined effects of exercise and electrical stimulation in longitudinal clinical trials, particularly in injury models aside from ACL injury. Based on this and previous data, we recommend TENS as an intervention to modify neural excitability in patients with CAI, and posit that its combination with therapeutic exercise may serve to translate these physiologic changes into functional changes.

Ethical approval

This study was approved by the Appalachian State University Institutional Review Board (Protocol #20−042) and followed guidance in line with the Declaration of Helsinki.

Conflict of interest

The authors have no conflicts of interest to report in relation to this publication.

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