

## Age Group Comparisons of TENS Response Among Individuals With Chronic Axial Low Back Pain

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**Abstract:** Chronic low back pain (CLBP) is a highly prevalent and disabling musculoskeletal pain condition among older adults. Transcutaneous electrical nerve stimulation (TENS) is commonly used to treat CLBP, however response to TENS in older adults compared with younger adults is untested. In a dose-response study stratified by age, 60 participants with axial CLBP (20 young, 20 middle-aged, 20 older) received four 20-minute sessions of high-frequency high-intensity TENS over a 2- to 3-week period in a laboratory-controlled setting. Experimental measures of pain sensitivity (mechanical pressure pain detection threshold) and central pain excitability (phasic heat temporal summation and heat aftersensations) were assessed before and after TENS. Episodic or immediate axial CLBP relief was assessed after TENS via measures of resting pain, movement-evoked-pain, and self-reported disability. Cumulative or prolonged axial CLBP relief was assessed by comparing daily pain reports across sessions. Independent of age, individuals experienced episodic increase in the pressure pain detection threshold and reduction in aftersensation after TENS application. Similarly, all groups, on average, experienced episodic axial CLBP relief via improved resting pain, movement-evoked pain, and disability report. Under this design, no cumulative effect was observed as daily pain did not improve for any age group across the 4 sessions. However, older adults received higher TENS amplitude across all sessions to achieve TENS responses similar to those in younger adults. These findings suggest that older adults experience similar episodic axial CLBP relief to that of younger individuals after high-frequency, high-intensity TENS when higher dose parameters are used.

**Perspective:** This study examined age group differences in experimental and axial CLBP response to TENS, delivered under the current recommended parameters of strong, but tolerable amplitude. Older adults had comparable TENS response although at higher TENS amplitude than younger adults, which may have important mechanistic and clinical implications.

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**Key words:** Age, axial, low back pain, transcutaneous electrical nerve stimulation.

Chronic low back pain (CLBP) is a prevalent condition among older adults and a major contributor to the exponential increase in the use of pain management.<sup>10,36,37,66</sup> Pharmacologic treatment is commonly prescribed for CLBP, however, such methods are controversial among older adults due to the potential for higher health risks.<sup>3</sup> Alternatively, transcutaneous

electrical nerve stimulation (TENS) may be more suitable for older adults because it is a conservative, nonpharmacologic treatment for CLBP. TENS has been studied extensively and quantification of past studies has given mixed results.<sup>27,30,40,64</sup> However, recent clinical research has advanced our understanding of TENS efficacy in important ways. Specifically, TENS appears to be more

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effective for movement-evoked versus resting pain and requires a high-intensity stimulus (ie, strong, yet tolerable).<sup>39,47,52,62</sup> However, the efficacy of such parameters based on age remains uninvestigated.

Mechanistic research has elucidated age-related changes in laboratory correlates of central pain excitability. Specifically, older adults are reported to have enhanced pain facilitation, whereby application of a repetitively delivered painful stimulus is perceived to be progressively more painful despite unchanging intensity of the stimulus.<sup>12,33</sup> Older adults have also demonstrated attenuated pain inhibition such that pain reduction after a painful stimulus is either less than or slower than that in younger adults.<sup>13,31,49,65</sup> Collectively, these findings suggest that age-related neuroplastic changes may reduce the capability of older adults to respond to pain-relieving treatments such as TENS because the mechanism of action includes activation of the central descending inhibitory pain system.<sup>52,54,61</sup>

Therefore, our purpose was to test whether response to high-frequency, high-intensity TENS differed by age group among individuals with axial CLBP. This study had 2 principal aims. The first aim was to assess age differences in experimental pain response to TENS during rest. We hypothesized that older adults with axial CLBP would have decreased response to TENS due to enhanced pain facilitation and reduced pain inhibition.<sup>32</sup> The second aim was to assess age group differences in CLBP measures of TENS response, including resting pain, movement-evoked pain, and disability. Although studies have yet to compare response to TENS for CLBP across age groups, we anticipated that older adults would have a reduced response based on

age-related changes in the descending inhibitory pain system.<sup>32</sup> In addition, this study had 2 exploratory aims. The first was to assess daily pain across multiple TENS treatment sessions to ascertain whether the effects of TENS were cumulative under the current design. The second was to assess age group differences in TENS amplitude to provide a preliminary indication of dose and response by age group using a standard stimulus intensity instruction set. The overarching goal of this study was to determine age-specific effects of TENS using both experimental pain and axial CLBP self-report measures to provide novel information regarding the pain reduction capacity of TENS among older adults.

## Methods

### Study Population

Simple purposive sampling stratified to a priori age group quotas was used to enroll screened participants with axial CLBP (Fig 1). Once adequate group sampling had occurred, enrollment to that particular age group ceased. All participants were not currently seeking care and were recruited from the community via printed advertisements. In addition, a community health program that linked research opportunities with prospective participants via social and media services was used. Participants were categorized based on the following age groups: young (18–39 years old), middle-aged (40–56 years old), and older (57–79 years old). Age group ranges were determined a priori based on previous research.<sup>31,48</sup> This study was approved by the University

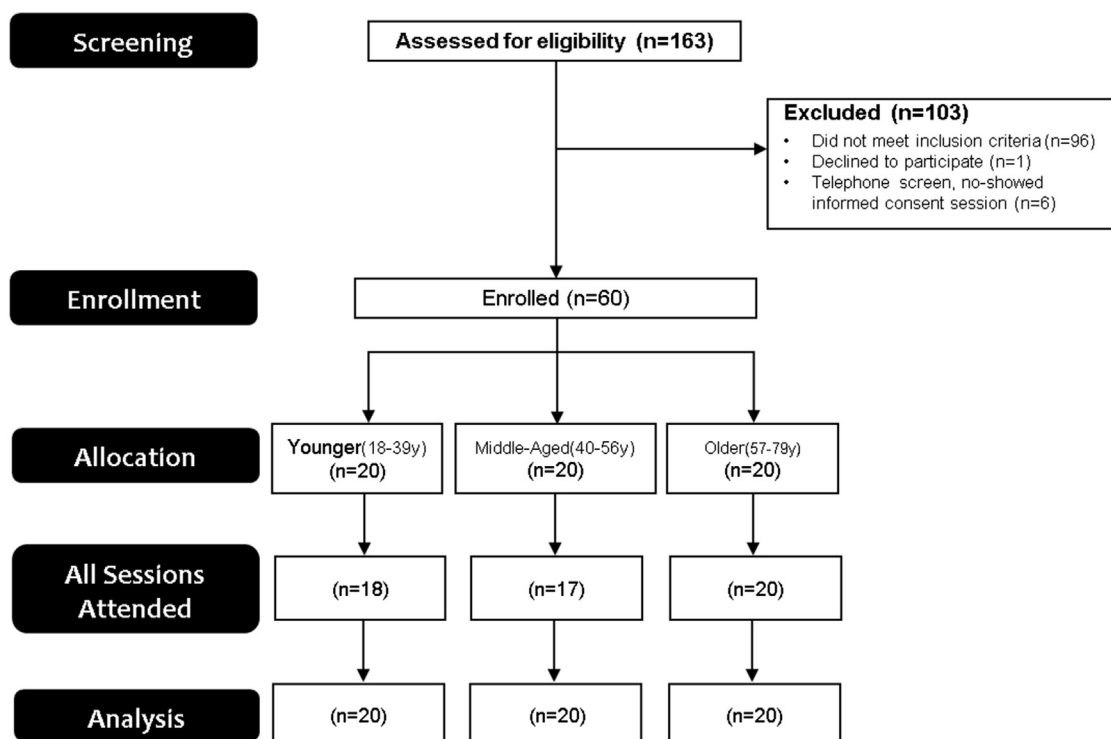


Figure 1. Flow diagram of patient enrollment.

of Florida Institutional Review Board and all participants provided written informed consent before enrollment.

### Inclusion and Exclusion Criteria

Individuals were considered for inclusion in the study if they had experienced axial CLBP for at least 3 months; CLBP also had to be their primary complaint. In addition, average daily pain intensity was required to be equal to or greater than 40 at worst on a scale of 0 to 100 (0 = no pain, 100 = worst pain imaginable) to ensure that individuals were experiencing a moderate level of axial CLBP. Individuals were excluded if they had 1) symptoms of lower extremity nerve root involvement such as motor weakness and sensory disturbance; 2) axial CLBP resulting from trauma (eg, car accident, work accident, fall); 3) treatment for CLBP by any health care professional (eg, doctor, chiropractor, physical therapist) within the past month; 4) previous surgery for low back musculoskeletal pain; 5) used opioids; 6) comorbidities including uncontrolled hypertension, diabetic neuropathy, circulatory disorders interfering with activities of daily living, cardiac event history (eg, myocardial infarction), or epilepsy; 7) an implanted cardiac pacemaker; 8) been admitted to a psychiatric-related hospital within the past year; or 8) positive pregnancy test. In addition, prospective participants were screened for cognitive impairment before the informed consent procedure, which was determined by a score lower than 23 on the Mini Mental State Examination.<sup>15</sup> Participants aged 70 years or older also underwent a brief neurological test to ensure intact sensory function.<sup>11</sup>

### Procedures

A dose-response design stratified by the aforementioned age groups of young, middle-aged, and older participants was used. The intent was to examine age group differences in the effects of TENS provided clinically using the current dosing recommendations.<sup>52,61</sup> Therefore, a placebo arm was not included in this analysis. Participants completed 5 experimental sessions over a 3- to 4-week period (TENS provided in visits 1–4), with up to 2 sessions completed per week. The weekly intervention frequency is similar to a seminal TENS efficacy trial performed among individuals with CLBP.<sup>38</sup> Testing was conducted by the same experimenter in a single climate-controlled laboratory at the same time of day across all sessions. Participants completed intake questionnaires (demographic and pain) and were assessed

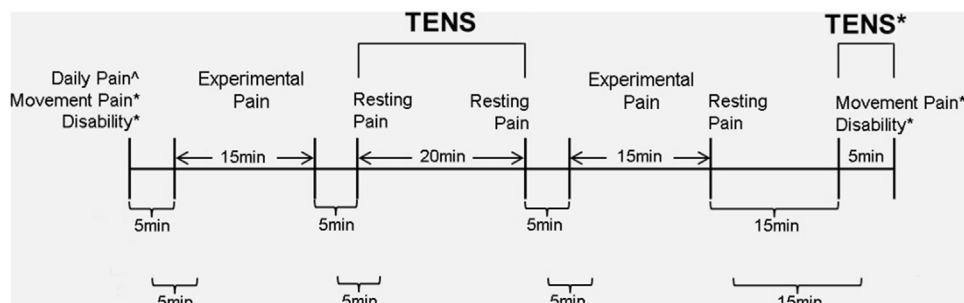
Age, TENS Response, and Low Back Pain

for movement-evoked pain intensity and self-reported disability at the beginning of session 1. The study procedures are outlined in Fig 2. In each of the first 4 sessions, participants were assessed for resting and experimental pain response after a 20-minute application of TENS to the lumbar spine in a resting position. In addition, movement-evoked pain and self-reported disability were assessed with and without TENS application at the end of the first session only. Daily pain was assessed at the beginning of all 5 sessions.

### Experimental Pain Response

Pressure pain detection threshold (PPT) assessed local pain sensitivity and was performed by applying 1-kg force/cm<sup>2</sup>/second using a Wagner Force Ten FDX 25 Digital Force Gauge with a 1-cm<sup>2</sup> flat rubber tip (Wagner Instruments, Greenwich, CT). Experimenters were proficient with PPT testing through application in patient care and in previous clinical trials. The PPT site was the posterior superior iliac spine (PSIS) bilaterally. Before testing, the participants were educated on PPT; this included visualization of the testing unit and its application. On testing, the participants were instructed to indicate when pressure first became painful (first onset of pain) by verbalizing the word "pain." To improve testing precision, 3 trials were performed at each PSIS, with the last 2 ratings at each site averaged to calculate a PPT score. PPT has been shown to have excellent test-retest reliability in axial regions.<sup>28</sup> Furthermore, previous research has shown higher PPTs for older adults,<sup>18,32</sup> as well as increased local PPTs after TENS.<sup>8,45,62</sup>

Phasic heat temporal summation (TS) provided an indication of changes in central pain excitability<sup>67</sup> and was measured using a 3-cm<sup>2</sup> thermode connected to a PATHWAY Model contact heat-evoked potential stimulator (Medoc Advanced Medical Systems, Ramat Yishai, Israel). Five consecutive 50°C heat pulses at .33 Hz interstimulus interval were delivered to the plantar aspect of the right foot, posterior to the first metatarsophalangeal joint. Participants rated the second pain they felt after each heat pulse using the numeric pain rating scale (NPRS), with 0 equal to "no pain" and 100 equal to "worst pain imaginable." TS was determined using the established calculation of the absolute difference between the fifth and first pain ratings.<sup>1,23,50</sup> Individuals reporting 100/100 NPRS during TS were removed from the analysis because 1) the extent of summation cannot be observed, and 2) the ratings are more likely an



**Figure 2.** Study procedures. \*Assessed over 5 sessions; \*Assessed at session 1 only.

indication of A-delta pain transmission (first pain). Previously, healthy older adults have shown enhanced TS compared with younger adults.<sup>12,33</sup> Specific to the TENS response, TS has not previously changed after TENS,<sup>62</sup> although Liebano et al<sup>35</sup> found changes in temporal summation of pain from mechanical stimuli. Collectively, a paucity of studies have assessed TS effects (either heat or mechanical) from TENS and, to our knowledge, none have assessed age differences or involved an axial CLBP cohort.

Aftersensations (AS) are an additional measure of central pain excitability change that can be assessed using experimental pain models.<sup>22,67</sup> Prolonged aftersensations have been observed among older adults<sup>49</sup> and individuals with chronic pain conditions.<sup>56-58</sup> Contact heat was delivered by a 3-cm<sup>2</sup> thermode connected to a PATHWAY Model advanced thermal stimulator (Medoc Advanced Medical Systems, Ramat Yishai, Israel). Response to a 15-second stimulus at the first session determined the tonic heat stimulus temperature (46°C, 47°C, or 48°C) corresponding to a pain rating of 50/100 NPRS, which was then used for all sessions. For AS, a 30-second tonic heat stimulus was applied to the plantar aspect of the right foot, posterior to where TS was assessed. Next, the temperature was decreased at a rate of 10°C/second to a neutral temperature (33°C), during which time individuals provided pain intensity ratings (0–100 NPRS) every 2 seconds for a total of 10 seconds. The 5 corresponding pain ratings were then entered into a trapezoidal area-under-the-curve (AUC) formula<sup>43</sup> to calculate AS.

### **Axial CLBP Measures**

Episodic dependent measures included resting pain, movement-evoked pain, and self-reported disability; the cumulative effects dependent measure was daily pain. Resting pain was CLBP pain intensity rated on an NPRS of 0 to 100, which is a responsive measure in pain assessment.<sup>9</sup> Movement-evoked pain was assessed using the Back Performance Scale (BPS).<sup>59</sup> During the BPS, participants performed 5 functional tasks specific to the spine, including 1) grasping the toes with the fingertips in a sitting position; 2) forward bending from standing; 3) picking up paper from standing; 4) long sitting from supine; and 5) lifting a 5-kg box from the floor to a table repeatedly. Participants provided a pain intensity rating after each task (0–100 NPRS) and the 5 pain ratings were averaged to calculate movement-evoked pain. Disability was the cumulative score of the BPS ranging from 0 (no disability) to 15 (maximum disability).<sup>59</sup> Scores for each task ranged from 0 to 3, with 0 indicating the ability to perform the task without difficulty and 3 indicating the inability or unwillingness to perform the task, or maximum difficulty with the task. Daily pain was assessed using the Brief Pain Inventory Short Form, which is a 10-point numeric scale to measure the best and worst pain intensity over the previous 24 hours, the average pain intensity, and the present pain intensity.<sup>60</sup> A mean of the 4 ratings served as the daily pain score for each session.

### **TENS Intervention**

TENS was delivered using dual-channel, portable, electrical stimulation units with 2 leads and 4 carbon-cloth electrodes (EMPI Select TENS Pain Management System, DJO Inc, St. Paul, MN). Units were calibrated by the manufacturer before delivery. The TENS waveform was balanced asymmetrical at a frequency of 125 Hz. Pulse duration was variable based on intensity, ranging between 16 and 360 microseconds. To control for positional intolerance during the intervention, the participants were given the option of reclining, lying prone, or lying on their side with appropriate pillow support. The body position selected for TENS was maintained across all sessions. Electrode placement paralleled clinical application in that the electrodes were placed immediately above and below the spinal level corresponding to the pain complaint. However, we opted to use a crossed pattern of electrode placement whereby channel electrodes were on opposite sides (left/right) and level (high/low) of the spine (Fig 3). This was intended to align with a previous study by Vance et al,<sup>62</sup> in which similar electrode positions were used to intersect the knee joint in an osteoarthritic cohort.

TENS application was not blinded based on age because this was not feasible in the current research design. However, all TENS application was done in a standard manner and participants were blinded to the channel intensity, which was set by a licensed physical therapist by increasing both channels simultaneously at a rate of 1 mA/second. Participants were instructed to verbalize when a “strong, but tolerable and not painful” stimulus was experienced, which should correspond with a 70/100 stimulus intensity (0 equal to “no sensation” and 100 equal to “intolerable sensation”). Although 70/100 is an arbitrary intensity level, we aimed to ensure the stimulus was stronger than moderate but not intolerable. Furthermore, a numeric anchor may improve the homogeneity of stimulus perception above and beyond a strength descriptor. At the same time, an additional stop rule was in place to ensure TENS did not evoke a motor stimulus. Once the channel intensity surpassed 15 mA, the physical therapist palpated the lumbar paraspinals in the region of the electrodes. If motor activation was detected, the channel intensity was decreased by 10% as has been previously used in studies on the effects of TENS.<sup>46,62</sup> Once the stimulus intensity was set, TENS remained on for 20 minutes.<sup>62</sup>

At the first session, TENS was also applied during the BPS to assess movement-evoked pain and self-reported disability response. TENS electrodes were reapplied as described above with participants in a standing position. Channel intensity was increased to the level corresponding to TENS during rest. Participants then performed the 5 tasks of the BPS and verbalized movement-evoked pain (0–100 NPRS) after each task, while a rater scored disability using the 0–15 BPS scale.

### **Statistical Analysis**

Analyses were completed using IBM SPSS Statistics software, version 21 (IBM, Armonk, NY). The alpha level





**Figure 3.** TENS unit and setup. Four carbon electrode pads are affixed to the patient's low back region (right) in a crossed-electrode pattern, and connected via 2 leads to the EMPI TENS Select unit (left).

was set at  $P = .05$  for all analyses. We could not power this study based on previous studies examining TENS effects based on age groups, since to our knowledge none have been performed. However, Larivière et al<sup>31</sup> observed change in attenuated experimental pain for older adults compared with younger and middle-aged adults in sample sizes of 20. Furthermore, Marchand et al<sup>38</sup> observed greater reduction in TENS for individuals with CLBP ( $n = 14$ ) versus placebo TENS ( $n = 12$ ), albeit in controlled samples. Therefore, 3 age group samples of 20 individuals ( $n = 60$ ) were deemed adequate to observe changes in experimental and clinical pain after TENS, and by age group. Separate multivariate mixed-model ANOVAs were created to assess age-related change in experimental pain response across sessions for each test (PPT, TS, AS), with age group as the between-subject factor and time (pre-TENS, post-TENS) and session ( $n = 4$ ) as the within-subject factors. The Box M and Levene tests examined homogeneity of variances and covariances across dependent variables. The Mauchly test examined model sphericity, and Greenhouse-Geisser correction was used in the presence of sphericity violation. The Bonferroni test was used to assess pairwise comparisons as this is an established, conservative method of controlling for familywise error.

Similar multivariate mixed-model ANOVAs tested age response in resting pain, movement-evoked pain, and disability across sessions. For resting pain, age group was the between-subject factor, and time (pre-TENS, post-TENS, 20 minutes post-TENS) was the within-subject factor. In addition, change in resting pain was examined across all sessions with session ( $n = 4$ ) the within-subject factor. Disability and movement-evoked pain were assessed using similar methods, albeit within

a single session. Movement-evoked pain was the average pain intensity (NPRS) during performance of the 5 BPS tasks, and disability was the BPS composite score. For both models, age group was the between-subject factor, and condition (BPS tasks with and without TENS) was the within-subject score.

For exploratory analyses, change in cumulative daily pain across sessions was assessed using the Brief Pain Inventory Short Form score. Group served as the between-subject factor, and session ( $n = 5$ ) served as the within-subject factor. Daily pain was collected on a fifth occasion after the final TENS session to determine cumulative effects beyond the immediate effects from the fourth session. Assumption testing and pairwise comparisons for all models were similar to those used in experimental pain response models. For age group differences in TENS amplitude, univariate ANOVA was performed for each session. Change in TENS amplitude across sessions was then examined using mixed-model ANOVA, with age group as the between-group factor and session ( $n = 4$ ) as the within-group factor.

## Results

Sixty individuals were enrolled from September 2013 to October 2014 (Fig 1). Groups were similar in the proportion of females, income, and axial CLBP characteristics, but different in age (planned) and education (Table 1). In total, 92% ( $n = 55$ ) of participants completed all testing sessions, and 95% ( $n = 57$ ) completed 4 of the 5 sessions. Attrition was due to either not completing all sessions within the allotted 4-week time frame ( $n = 2$ ) or being withdrawn due to noncompliance with the attendance policy ( $n = 3$ ).

**Table 1. Intake Characteristics by Age Group**

FACTOR	YOUNG (N = 20)	MIDDLE-AGED (N = 20)	OLDER (N = 20)	P
Age, y	30.65 (6.41)	48.85 (4.45)	63.50 (5.34)	<.001*
Female, %	75	65	65	.735
Education, %				
Less than high school diploma	10	20	20	.020†
High school diploma	10	45	20	
College attendance	80	35	70	
Income, %				
<\$20,000	55	70	42	.509
\$20,001–\$50,000	25	20	32	
>\$50,000	20	10	26	
Pain-relieving medication, %	20	25	25	.911
Tobacco use, %	25	45	25	.292
Caffeine use, %	75	85	75	.675
Axial CLBP measures				
Pain duration, wk	208.15 (180.19)	280.32 (344.32)	255.60 (343.13)	.745
Daily pain intensity, 0–10	4.96 (1.60)	4.89 (1.94)	4.51 (2.05)	.720
Movement-evoked pain intensity, 0–100	39.52 (22.68)	39.90 (25.24)	33.15 (27.57)	.639
Disability, 0–15	4.80 (2.35)	6.25 (3.25)	6.05 (3.35)	.266

Values in parentheses are the standard deviation.

\*Different across all groups, significant at  $P < .001$ .

†Different between the younger and middle-aged groups, significant at  $P < .05$ .

## Experimental Pain Response

Experimental pain response after TENS is outlined in Table 2. Independent of age group, PPT increased at the first ( $F_{1,57} = 12.51$ ,  $P < .01$ ), second ( $F_{1,54} = 9.49$ ,  $P < .01$ ), third ( $F_{1,54} = 4.24$ ,  $P < .05$ ), and fourth ( $F_{1,54} = 14.47$ ,  $P < .001$ ) sessions after TENS. The lone interaction for PPT was age group by time (pre-TENS, post-TENS) at the fourth session ( $F_{2,54} = 3.83$ ,  $P < .05$ ). Pairwise comparisons revealed that at this session, the larger rate of change occurred for older adults versus younger and middle-aged adults.

Independent of age group, AS decreased at the first ( $F_{1,55} = 17.33$ ,  $P < .001$ ), second ( $F_{1,54} = 19.16$ ,  $P < .001$ ), third ( $F_{1,53} = 4.04$ ,  $P < .05$ ), and fourth ( $F_{1,52} = 5.10$ ,  $P < .05$ ) sessions. The lone interaction for AS was time by session ( $F_{3,47} = 5.10$ ,  $P < .05$ ). Pairwise comparisons revealed that the AS response was higher in the first session compared to the third session. TS was not found to change within or across sessions, or across age groups after TENS ( $P > .05$ ).

## Axial CLBP Response

Age group interactions did not exist for resting pain, movement-evoked pain, or disability ( $P > .05$ ). Resting pain changed for all groups during the first ( $F_{2,56} = 22.24$ ,  $P < .001$ ), second ( $F_{2,52} = 18.96$ ,  $P < .001$ ), third ( $F_{2,53} = 18.60$ ,  $P < .001$ ), and fourth ( $F_{2,53} = 18.20$ ,  $P < .001$ ) sessions. Pairwise comparisons revealed post-TENS resting pain and 20 min post-TENS resting pain to be lower than pre-TENS resting pain at all sessions, although not significantly different from each other (Fig 4). Movement-evoked pain ( $F_{1,54} = 35.81$ ,  $P < .001$ ; Fig 5) and disability ( $F_{1,54} = 18.90$ ,  $P < .001$ ) also improved with TENS during BPS tasks compared with no TENS. Daily

pain was not observed to change across sessions either by age or for the entire axial CLBP cohort ( $P > .05$ ).

## TENS Amplitude

Older adults were observed to have higher TENS amplitude compared with younger and middle-aged adults at the first ( $F_{2,59} = 11.89$ ,  $P < .001$ ), second ( $F_{2,56} = 12.71$ ,  $P < .001$ ), third ( $F_{2,56} = 13.67$ ,  $P < .001$ ), and fourth ( $F_{2,56} = 13.76$ ,  $P < .001$ ) sessions. TENS amplitude did not change across sessions, either by group or for the entire CLBP sample ( $P > .05$ ; Fig 6). Collapsed across sessions, older adults had a mean of 25.3 mA (standard deviation [SD] = 14.1) compared with 7.9 mA (SD = 8.4) and 9.6 mA (SD = 6.8) for younger and middle-aged adults, respectively.

## Discussion

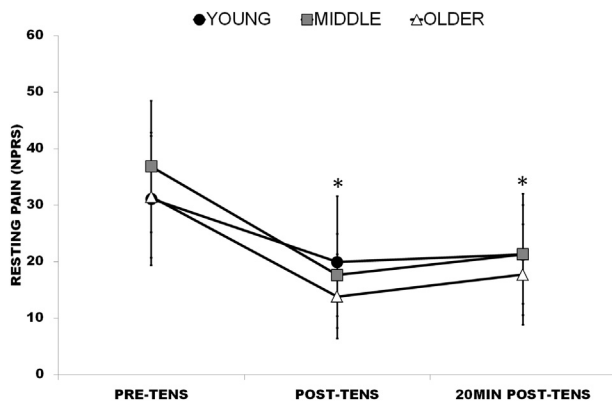
In the current study, we found that TENS evoked similar changes in experimental pain responses across all age groups, suggesting improved pain sensitivity and reduced central pain excitability. Similarly, older adults showed similar episodic improvements in resting pain, movement-evoked pain, and disability compared with younger cohorts. Therefore, age-related neuroplastic changes to the pain system may not be severe enough to render nonpharmacologic pain modulation obsolete. However, older adults demonstrated higher TENS amplitude in conjunction with these effects, which may be an indication of the dose required to reach pain inhibition potential. Furthermore, because a higher dose may be needed for older adults to achieve a similar response to TENS as younger adults, the former may be routinely underdosed when perception-based instructions of strong but tolerable are not used to set TENS amplitude.

**Table 2. Experimental Pain Response After TENS by Session**

MEASURE	SESSION 1		SESSION 2		SESSION 3		SESSION 4	
	MEAN CHANGE (95% CI)	P	MEAN CHANGE (95% CI)	P	MEAN CHANGE (95% CI)	P	MEAN CHANGE (95% CI)	P
PPT								
Young	.46 (.08, .84)	.436	.34 (−.05, .74)	.362	.21 (−.14, .56)	.588	.19 (−.19, .57)	.028*
Middle-aged	.19 (−.19, .57)		.14 (−.22, .50)		.08 (−.27, .42)		.20 (−.16, .56)	
Older	.52 (.14, .90)		.51 (.15, .87)		.32 (−.01, .66)		.82 (.45, 1.20)	
Total	.39 (.17, .61)	.001	.33 (.12, .55)	.003	.20 (.01, .40)	.044	.41 (.19, .62)	<.001
TS								
Young	4.76 (−3.99, 13.52)	.571	−2.77 (−11.30, 5.77)	.870	.17 (−6.80, 7.14)	.463	.13 (−5.57, 5.82)	.556
Middle-aged	6.44 (−2.10, 14.95)		.32 (−7.75, 8.38)		−3.35 (−3.82, 10.52)		−3.74 (−8.97, 1.49)	
Older	.45 (−7.62, 8.52)		−.94 (−9.23, 7.34)		−2.79 (−3.99, 9.57)		.83 (−4.54, 6.21)	
Total	3.89 (−.99, 8.76)	.116	−1.13 (−5.92, 3.66)	.638	−.13 (−4.16, 3.90)	.948	−.93 (−4.07, 2.21)	.427
AS								
Young	−27.14 (−.96, −53.32)	.925	−33.12 (−6.58, −59.66)	.600	−14.97 (.26, −30.20)	.562	−8.81 (7.94, −25.56)	.112
Middle-aged	−29.70 (−4.86, −54.54)		−39.73 (−15.26, −64.19)		−7.08 (8.15, −22.31)		.58 (16.88, −15.72)	
Older	−34.20 (−9.31, −58.99)		−22.35 (−4.86, −54.54)		−3.93 (18.37, −10.52)		−24.14 (−7.39, −40.88)	
Total	−30.33 (−15.73, −44.93)	<.001	−31.73 (−17.20, −46.27)	<.001	−8.66 (−.02, −17.31)	.049	−10.78 (−1.21, −20.37)	.028

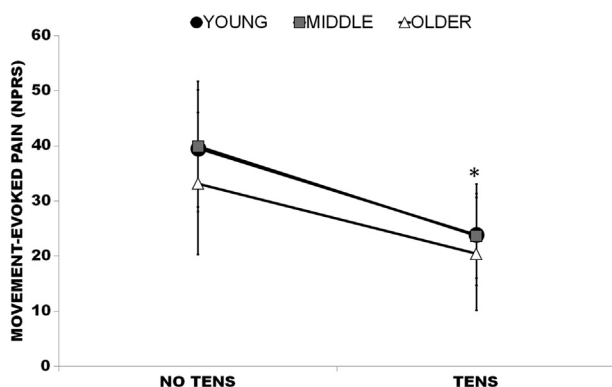
Mean change refers to the mean change after TENS (95% confidence interval of change reported in parentheses). The *P* value for the age groups is the significance value of the age by time interaction. The *P* values for the total is the significance of the time main effect (before and after TENS).

\*PPT change in older group only.

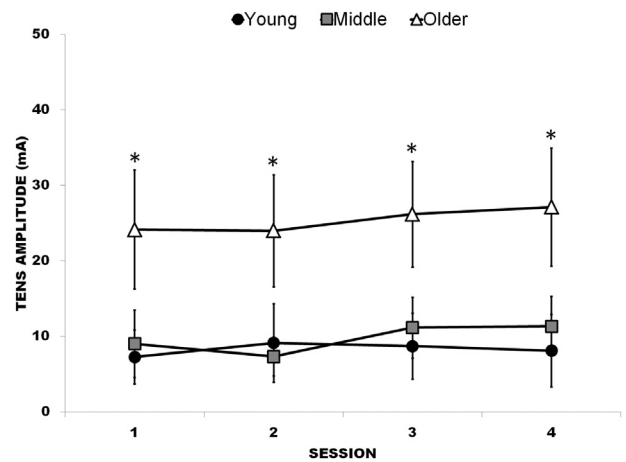


**Figure 4.** Resting pain rating change with TENS by age group, sessions collapsed. \*Significant difference from pre-TENS. Error bars indicate the 95% confidence interval.

Independent of age, reduction in pain sensitivity (PPT) with TENS corroborates a wealth of previous research.<sup>6,8,35,39,42,45,46</sup> By comparison, the observed changes in central pain excitability with TENS are less understood. Dailey et al<sup>8</sup> reported that TENS restored conditioned pain modulation in individuals with fibromyalgia, which suggests normalization of pain inhibitory function. To our knowledge, the present study is the first to examine the effects of TENS on AS, and our findings align with the Dailey et al study. However, we observed minimal effects on TS (another measure of central pain excitability), which was also reported in a previous study of individuals with knee osteoarthritis.<sup>62</sup> The authors of that study proposed that heat pain stimulus response may reflect cutaneous hyperalgesia, which could have limited effects from TENS. In contrast, mechanical TS has reduced with TENS, implying either potential differential effects from deep-tissue hyperalgesia (as previously suggested<sup>46,62</sup>) or a larger activation of A-delta fibers versus c-fibers. Nevertheless, current and previous findings imply some capacity for TENS to influence laboratory correlates of central excitability, which align with previous mechanistic work examining descending (top down) TENS mechanisms in animals. Sluka et al and others<sup>29,53</sup> have found blocking activation of opioid



**Figure 5.** Movement-evoked pain ratings and concurrent TENS application by age group. \*Significant difference from no TENS. Error bars indicate the 95% confidence interval.



**Figure 6.** TENS amplitude across all sessions by age group. Error bars indicate the 95% confidence interval. \*Significant difference in the older group compared with the middle-aged and younger groups.

receptors in the rostroventral medulla inhibits the response to TENS. Similarly, the response to TENS has been linked to synaptic transmission in the midbrain periaqueductal gray area, as well as opioid, muscarinic, and  $\gamma$ -aminobutyric acid receptor activation in the spinal cord.<sup>61</sup>

Age-related differences in TENS amplitude likely occurred because older adults have a higher TENS perception threshold. TENS mechanisms are purported to induce a bottom-up response by activating large diameter afferent fibers,<sup>34,44</sup> and work in both animals and humans has determined multiple physiologic changes with age, including loss of these large fibers.<sup>18</sup> Furthermore, higher TENS perception among older adults is in line with experimental pain testing showing increases in the overall age-related pain threshold.<sup>18,32</sup> However, current findings are preliminary and do not indicate a direct relationship between TENS amplitude and either experimental or axial CLBP.

A second although less likely explanation for age-related differences in TENS amplitude was altered perceptions of the instruction set "strong, yet tolerable" and "not painful." Older adults have shown difficulty with certain rating scales, particularly related to sensory interpretation.<sup>16,17</sup> However, older adults reportedly do well with descriptive scales (ie, the McGill Pain Questionnaire).<sup>16,17</sup> Furthermore, scale comprehension was likely enhanced by including a numeric anchor (70/100 stimulus intensity). This scale is similar to the NPRS for pain intensity, which is a valid tool for use among older adults.<sup>26</sup> In addition, TENS instruction was provided over multiple sessions rather than in a single session. If age group differences in TENS perception were the product of a learning effect, amplitude would have regressed toward the mean over time. However, differences in TENS amplitude remained constant over time for all age groups. Nevertheless, future psychometric investigations will confirm the appropriateness of this instruction set in older adults. Until such time, TENS dosing should remain perception based because lower-



intensity or set-dosing parameters may run the risk of underdosing older adults.

The TENS parameters used in this study demonstrated immediate (episodic) effects on pain, which may have important clinical implications for older adults. First, pharmacologic pain treatments are also episodic, but are less ideal for older adults due to increased health risks or potential mismanagement of care.<sup>5,41,55</sup> If future research determines that TENS episodic efficacy is similar to pharmacologic treatment, it may prove a viable, lower-risk alternative for axial CLBP. Second, episodic effects of TENS would have limited usefulness in clinical care, whereas wider access to TENS (home, community use) would potentially be more effective for axial CLBP because individuals could use as needed. A study by Chesterton et al<sup>7</sup> found limited added effects of home TENS in conjunction with primary care for tennis elbow. However, to our knowledge, research has not examined such an age-based model for CLBP. Compliance, safety, and outcomes among older adults require future trial assessment, although the usefulness and feasibility of TENS outside clinical care has already been proposed.<sup>52</sup> Furthermore, future research should consider the efficacy and effectiveness of TENS for outcomes other than pain that are specific to older adults or important to individuals. For example, a recent qualitative study by Gladwell et al<sup>20</sup> found factors such as distraction and relief of tension and spasm to be important factors for TENS use among individuals with chronic musculoskeletal pain.

In contrast to previous studies, we did not observe cumulative effects using the current design of sessions up to twice a week for 4 visits. A paucity of studies exists showing cumulative effects of TENS among participants with CLBP, although an elegant study by Marchand et al<sup>38</sup> observed a cumulative reduction in pain among participants with CLBP receiving TENS twice a week. However, the duration of TENS treatment was much longer than in the current study (10 weeks or 20 sessions). A more recent study by Facci et al<sup>14</sup> found cumulative pain reduction for CLBP after 10 TENS sessions within a 2-week period. Based on these findings, the potential for cumulative pain reduction using either increased frequency or a longer duration cannot be discounted. However, such treatment periods are outside the feasibility of most current supervised care models. Therefore, the potential for cumulative effects of TENS with greater frequency and/or duration is further argument for translation of access to TENS in home and community settings.

### Strengths and Limitations

There are strengths to our study, most notably a design specific to examining age-related differences in the response to TENS. Age is often included as a covariate without considering comorbidities, cognition, or the age appropriateness of measures. Moreover, studies often include only a small age range, whereas we included an even distribution across the lifespan (ie, age 20–74 years). Multiple axial CLBP measures were

used, and we were able to examine episodic versus cumulative effects of TENS. Finally, this study included an element of stimulus response allowing for age group comparisons of TENS amplitude.

There are also limitations to this study. We used TENS intervention methods similar to those used in previous studies,<sup>46,62</sup> however, we did not include a placebo arm. Therefore, we cannot discern active effects of TENS from nonspecific effects of treatment (eg, expectation, natural history) and this will be a high priority for future investigations using this age-based design. Second, pulse duration was variable rather than fixed, so intensity cannot be considered solely a product of increasing amplitude. However, previous animal work has downplayed pulse duration in the analgesic effects of TENS,<sup>21</sup> and variable pulse duration has been used previously to examine pain sensitivity response to TENS in humans.<sup>39</sup> Third, movement-evoked pain and disability were assessed at only 1 session to limit the number of TENS applications per session and over time. However, this precludes our assessment of change in movement-evoked pain and disability over time, which should be examined in future studies. Finally, despite adequate sample size to observe large effects of TENS, the study may have been underpowered to identify smaller effects. This should be considered when powering future studies.

### Future Directions

Although not uniform,<sup>8</sup> the majority of research shows that active TENS reduces pain above and beyond placebo TENS.<sup>4,35,46,62</sup> However, both expectation analgesia and TENS analgesia have overlapping mechanisms because opioid receptors are activated in multiple cortical and subcortical regions.<sup>63,68</sup> Because age-related pain neuroplasticity affects the same regions,<sup>18,19</sup> age-related change in expectation versus TENS analgesia should be determined by implementing a placebo arm in the current design.

Future studies should also examine age group differences in a more comprehensive examination of TENS dosing and response, either by within-group randomization of TENS amplitude or a standard amplitude across age groups. In addition, although lumbar pathoanatomic changes increase with age, pathology has not been strongly associated with pain severity or found to predict pain recovery.<sup>2,24,25,51</sup> However, use of imaging in future studies will elucidate whether interactions exist between pathology and TENS response among older adults.

Clinically, prospective studies will determine the effectiveness of TENS on axial CLBP among older adults in clinical settings, including as a preventative measure to chronicity or maintenance of function and quality of life. Finally, we indicate how a specific intervention fared across age groups, which is a novel design for assessing the efficacy of clinical treatment. This model may help to determine age-specific efficacy for other conservative treatments such as spinal-manipulative therapy, strength-training exercises, and acupuncture. Moreover,

comparison of age-specific efficacy across treatments will help to identify those that provide the greatest treatment response for older adults.

## Conclusions

With TENS, older adults with axial CLBP experienced episodic reduction of resting pain, movement-evoked pain, and improved function during spine-specific tasks. Pain reduction for all measures was similar to younger and middle-aged adults when dosing was based on perceived stimulation tolerance. These findings may be related to pain sensitivity or central pain excitability, because both measures improved with TENS, and older

adults demonstrated higher amplitude in conjunction with experiencing effects similar to younger individuals. Future studies will expand on these findings to determine age group differences in expectation versus active TENS response, associations between experimental pain and axial CLBP changes from TENS, and age group differences in (and effects from) TENS dosing.

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## References

- Anderson RJ, Craggs JG, Bialosky JE, Bishop MD, George SZ, Staud R, Robinson ME: Temporal summation of second pain: variability in responses to a fixed protocol. *Eur J Pain* 17:67-74, 2013
- Balagué F, Mannion AF, Pellisé F, Cedraschi C: Non-specific low back pain. *Lancet* 379:482-491, 2012
- Barber JB, Gibson SJ: Treatment of chronic non-malignant pain in the elderly. *Drug Saf* 32:457-474, 2009
- Barker R, Lang T, Steinlechner B, Mora B, Heigel P, Gauss N, Zimpfer M, Kober A: Transcutaneous electrical nerve stimulation as prehospital emergency interventional care: treating acute pelvic pain in young women. *Neuromodulation* 9:136-142, 2006
- Buckeridge D, Huang A, Hanley J, Kelome A, Reidel K, Verma A, Winslade N, Tamblyn R: Risk of injury associated with opioid use in older adults. *J Am Geriatr Soc* 58:1664-1670, 2010
- Chesterton LS, Foster NE, Wright CC, Baxter GD, Barlas P: Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects. *Pain* 106:73-80, 2003
- Chesterton LS, Lewis AM, Sim J, Mallen CD, Mason EE, Hay EM, van der Windt DA: Transcutaneous electrical nerve stimulation as adjunct to primary care management for tennis elbow: pragmatic randomised controlled trial (TATE trial). *BMJ* 347:f5160, 2013
- Dailey DL, Rakel BA, Vance CG, Liebano RE, Amrit AS, Bush HM, Lee KS, Lee JE, Sluka KA: Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain* 154:2554-2562, 2013
- Dannecker EA, George SZ, Robinson ME: Influence and stability of pain scale anchors for an investigation of cold pressor pain tolerance. *J Pain* 8:476-482, 2007
- Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG: Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 303:1259-1265, 2010
- Dutton M: *Orthopaedic Examination, Evaluation, and Intervention*, 2nd ed. New York, NY, McGraw-Hill Medical, 2008
- Edwards RR, Fillingim RB: Effects of age on temporal summation and habituation of thermal pain: clinical relevance in healthy older and younger adults. *J Pain* 2:307-317, 2001
- Edwards RR, Fillingim RB, Ness TJ: Age-related differences in endogenous pain modulation: a comparison of diffuse noxious inhibitory controls in healthy older and younger adults. *Pain* 101:155-165, 2003
- Facci LM, Nowotny JP, Tormem F, Trevisani VF: Effects of transcutaneous electrical nerve stimulation (TENS) and interferential currents (IFC) in patients with nonspecific chronic low back pain: randomized clinical trial. *Sao Paulo Med J* 129:206-216, 2011
- Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189-198, 1975
- Gagliese L: Pain and aging: the emergence of a new sub-field of pain research. *J Pain* 10:343-353, 2009
- Gagliese L, Katz J: Age differences in postoperative pain are scale dependent: a comparison of measures of pain intensity and quality in younger and older surgical patients. *Pain* 103:11-20, 2003
- Gibson SJ, Farrell M: A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin J Pain* 20:227-239, 2004
- Gibson SJ, Weiner DK: *Pain in older persons*. Seattle, WA, IASP Press, 2005
- Gladwell PW, Badlan K, Cramp F, Palmer S: Direct and indirect benefits reported by users of transcutaneous electrical nerve stimulation for chronic musculoskeletal pain: qualitative exploration using patient interviews. *Phys Ther*, 2015
- Gopalkrishnan P, Sluka KA: Effect of varying frequency, intensity, and pulse duration of transcutaneous electrical nerve stimulation on primary hyperalgesia in inflamed rats. *Arch Phys Med Rehabil* 81:984-990, 2000
- Gottrup H, Kristensen AD, Bach FW, Jensen TS: Aftersensations in experimental and clinical hypersensitivity. *Pain* 103:57-64, 2003
- Granot M, Granovsky Y, Sprecher E, Nir R-R, Yarnitsky D: Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation. *Pain* 122:295-305, 2006
- Haig AJ, Geisser ME, Tong HC, Yamakawa KS, Quint DJ, Hoff JT, Chiodo A, Miner JA, Phalke VV: Electromyographic and magnetic resonance imaging to predict lumbar stenosis, low-back pain, and no back symptoms. *J Bone Joint Surg Am* 89:358-366, 2007

25. Haig AJ, Tong HC, Yamakawa KS, Parres C, Quint DJ, Chiodo A, Miner JA, Phalke VC, Hoff JT, Geisser ME: Predictors of pain and function in persons with spinal stenosis, low back pain, and no back pain. *Spine* 31:2950-2957, 2006
26. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, Fainsinger R, Aass N, Kaasa S: Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage* 41:1073-1093, 2011
27. Johnson MI, Walsh DM: Pain: continued uncertainty of TENS' effectiveness for pain relief. *Nat Rev Rheumatol* 6: 314-316, 2010
28. Jones DH, Kilgour RD, Comtois AS: Test-retest reliability of pressure pain threshold measurements of the upper limb and torso in young healthy women. *J Pain* 8: 650-656, 2007
29. Kalra A, Urban MO, Sluka KA: Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS). *J Pharmacol Exp Ther* 298:257-263, 2001
30. Khadilkar A, Odebiyi DO, Brosseau L, Wells GA: Transcutaneous electrical nerve stimulation (TENS) versus placebo for chronic low-back pain. *Cochrane Database Syst Rev*;CD003008, 2008
31. Larivière M, Goffaux P, Marchand S, Julien N: Changes in pain perception and descending inhibitory controls start at middle age in healthy adults. *Clin J Pain* 23:506-510, 2007
32. Lautenbacher S: Experimental approaches in the study of pain in the elderly. *Pain Med* 13:S44-S50, 2012
33. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L: Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain* 115:410-418, 2005
34. Levin MF, Hui-Chan CW: Conventional and acupuncture-like transcutaneous electrical nerve stimulation excite similar afferent fibers. *Arch Phys Med Rehabil* 74:54-60, 1993
35. Liebano RE, Rakel B, Vance CGT, Walsh DM, Sluka KA: An investigation of the development of analgesic tolerance to TENS in humans. *Pain* 152:335-342, 2011
36. Manchikanti L, Falco FJE, Singh V, Pampati V, Parr AT, Benjamin RM, Fellows B, Hirsch JA: Utilization of interventional techniques in managing chronic pain in the Medicare population: analysis of growth patterns from 2000 to 2011. *Pain Physician* 15:E969-E982, 2012
37. Manchikanti L, Singh V, Pampati V, Smith HS, Hirsch JA: Analysis of growth of interventional techniques in managing chronic pain in the Medicare population: a 10-year evaluation from 1997 to 2006. *Pain Physician* 12:9-34, 2009
38. Marchand S, Charest J, Li J, Chenard JR, Lavignolle B, Laurencelle L: Is TENS purely a placebo effect? A controlled study on chronic low back pain. *Pain* 54:99-106, 1993
39. Moran F, Leonard T, Hawthorne S, Hughes CM, McCrum-Gardner E, Johnson MI, Rakel BA, Sluka KA, Walsh DM: Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity. *J Pain* 12:929-935, 2011
40. Nnoaham KE, Kumbang J: Transcutaneous electrical nerve stimulation (TENS) for chronic pain. *Cochrane Database Syst Rev*;CD003222, 2008
41. Pahor M, Guralnik JM, Wan JY, Ferrucci L, Penninx BW, Lyles A, Ling S, Fried LP: Lower body osteoarticular pain and dose of analgesic medications in older disabled women: the Women's Health and Aging Study. *Am J Public Health* 89: 930-934, 1999
42. Pantaleão MA, Laurino MF, Gallego NL, Cabral CM, Rakel B, Vance C, Sluka KA, Walsh DM, Liebano RE: Adjusting pulse amplitude during transcutaneous electrical nerve stimulation (TENS) application produces greater hypoalgesia. *J Pain* 12:581-590, 2011
43. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH: 2 formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 28:916-931, 2003
44. Radhakrishnan R, Sluka KA: Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve stimulation-induced antihyperalgesia. *J Pain* 6: 673-680, 2005
45. Rakel BA, Zimmerman MB, Geasland K, Embree J, Clark CR, Noiseux NO, Callaghan JJ, Herr K, Walsh D, Sluka KA: Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: a randomized, blinded, placebo-controlled trial. *Pain* 155:2599-2611, 2014
46. Rakel B, Cooper N, Adams HJ, Messer BR, Frey Law LA, Dannen DR, Miller CA, Polehna AC, Ruggle RC, Vance CGT, Walsh DM, Sluka KA: A new transient sham TENS device allows for investigator blinding while delivering a true placebo treatment. *J Pain* 11:230-238, 2010
47. Rakel B, Frantz R: Effectiveness of transcutaneous electrical nerve stimulation on postoperative pain with movement. *J Pain* 4:455-464, 2003
48. Riley JL 3rd, Cruz-Almeida Y, Glover TL, King CD, Goodin BR, Sibille KT, Bartley EJ, Herbert MS, Sotolongo A, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB: Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *J Pain* 15:272-282, 2014
49. Riley JL 3rd, King CD, Wong F, Fillingim RB, Mauderli AP: Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. *Pain* 150:153-160, 2010
50. Robinson ME, Wise EA, Gagnon C, Fillingim RB, Price DD: Influences of gender role and anxiety on sex differences in temporal summation of pain. *J Pain* 5:77-82, 2004
51. Scheele J, Enthoven WT, Bierma-Zeinstra SM, Peul WC, van Tulder MW, Bohnen AM, Berger MY, Koes BW, Luijsterburg PA: Course and prognosis of older back pain patients in general practice: a prospective cohort study. *Pain* 154:951-957, 2013
52. Sluka KA, Bjordal JM, Marchand S, Rakel BA: What makes transcutaneous electrical nerve stimulation work? Making sense of the mixed results in the clinical literature. *Phys Ther* 93:1397-1402, 2013
53. Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A: Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J Pharmacol Exp Ther* 289: 840-846, 1999
54. Sluka KA, Walsh D: Transcutaneous electrical nerve stimulation: basic science mechanisms and clinical effectiveness. *J Pain* 4:109-121, 2003

55. Spitz A, Moore AA, Papaleontiou M, Granieri E, Turner BJ, Reid MC: Primary care providers' perspective on prescribing opioids to older adults with chronic non-cancer pain: a qualitative study. *BMC Geriatr* 11:35, 2011
56. Staud R, Koo E, Robinson ME, Price DD: Spatial summation of mechanically evoked muscle pain and painful after-sensations in normal subjects and fibromyalgia patients. *Pain* 130:177-187, 2007
57. Staud R, Vierck CJ, Robinson ME, Price DD: Overall fibromyalgia pain is predicted by ratings of local pain and pain-related negative affect—possible role of peripheral tissues. *Rheumatology (Oxford)* 45:1409-1415, 2006
58. Staud R, Weyl EE, Riley JL 3rd, Fillingim RB: Slow temporal summation of pain for assessment of central pain sensitivity and clinical pain of fibromyalgia patients. *PLoS One* 9:e89086, 2014
59. Strand LI, Moe-Nilssen R, Ljunggren AE: Back Performance Scale for the assessment of mobility-related activities in people with back pain. *Phys Ther* 82:1213-1223, 2002
60. Tan G, Jensen MP, Thornby JI, Shanti BF: Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain* 5:133-137, 2004
61. Vance CG, Dailey DL, Rakel BA, Sluka KA: Using TENS for pain control: the state of the evidence. *Pain Manag* 4: 197-209, 2014
62. Vance CG, Rakel BA, Blodgett NP, de Santana JM, Amendola A, Zimmerman MB, Walsh DM, Sluka KA: Effects of transcutaneous electrical nerve stimulation on pain, pain sensitivity, and function in patients with knee osteoarthritis: a randomized controlled trial. *Phys Ther* 92:898-910, 2012
63. Wager TD, Scott DJ, Zubieta J-K: Placebo effects on human mu-opioid activity during pain. *Proc Natl Acad Sci U S A* 104:11056-11061, 2007
64. Walsh DM, Howe TE, Johnson MI, Moran F, Sluka KA: Transcutaneous electrical nerve stimulation for acute pain. *Cochrane Database Syst Rev*:CD006142, 2009
65. Washington LL, Gibson SJ, Helme RD: Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. *Pain* 89:89-96, 2000
66. Weiner DK, Kim Y-S, Bonino P, Wang T: Low back pain in older adults: are we utilizing healthcare resources wisely? *Pain Med* 7:143-150, 2006
67. Woolf CJ: Central sensitization: implications for the diagnosis and treatment of pain. *Pain* 152:S2-S15, 2011
68. Zubieta J-K, Bueller JA, Jackson LR, Scott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS: Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 25:7754-7762, 2005