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Mapping Spinal Cord Stimulation-Evoked Muscle Responses in Patients With Chronic Spinal Cord Injury

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ABSTRACT

Objectives: Epidural spinal cord stimulation (eSCS) has shown promise for restoring some volitional motor control after spinal cord injury (SCI). Maximizing therapeutic response requires effective spatial stimulation generated through careful configuration of anodes and cathodes on the eSCS lead. By exploring the way the spatial distribution of low frequency stimulation affects muscle activation patterns, we investigated the spatial specificity of stimulation-evoked responses for targeted muscle groups for restoration after chronic SCI (cSCI) in participants in the Epidural Stimulation After Neurologic Damage (E-STAND) trial.

Materials and Methods: Fifteen participants with Abbreviated Injury Scale A cSCI from the E-STAND study were evaluated with a wide range of bipolar spatial patterns. Surface electromyography captured stimulation-evoked responses from the rectus abdominis (RA), intercostal, paraspinal, iliopsoas, rectus femoris (RF), tibialis anterior (TA), extensor hallucis longus (EHL), and gastrocnemius muscle groups bilaterally. Peak-to-peak amplitudes were analyzed for each pulse across muscles. Stimulation patterns with dipoles parallel (vertical configurations), perpendicular (horizontal configurations), and oblique (diagonal configurations) relative to the rostral-caudal axis were evaluated.

Results: Cathodic stimulation in the transverse plane indicated ipsilaterally biased activation in RA, intercostal, paraspinal, iliopsoas, RF, TA, EHL, and gastrocnemius muscles ($p < 0.05$). We found that caudal cathodic stimulation was significantly more activating only in the RF and EHL muscle groups than in the rostral ($p < 0.037$ and $p < 0.006$, respectively). Oblique stimulation was found to be more activating in the RA, intercostal, paraspinal, iliopsoas, and TA muscle groups than in the transverse ($p < 0.05$).

Conclusions: Cathodic stimulation provides uniform specificity for targeting laterality. Few muscle groups responded specifically to variation in rostral/caudal stimulation, and oblique stimulation improved stimulation responses when compared with horizontal configurations. These relations may enable tailored targeting of muscle groups, but the surprising amount of variation observed suggests that monitoring these evoked muscle responses will play a key role in this tailoring process.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT03026816.

Keywords: Electromyography, epidural spinal cord stimulation, spinal cord injury, spinal cord stimulation, volitional motor control

Conflict of Interest: Theoden I. Netoff and David P. Darrow hold equity in and serve as officers for Stim Sherpa, which has licensed optimization intellectual property from the University of Minnesota. The remaining authors reported no conflict of interest.

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INTRODUCTION

Tonic epidural spinal cord stimulation (eSCS), also known as epidural electrical stimulation, has been used to treat chronic pain for more than 50 years.[1,2] Although early reports of restored function after nontraumatic spinal cord injury (SCI) due to transverse myelitis or multiple sclerosis existed in the 1970s, more recent efforts have popularized exploration of eSCS to restore function after traumatic chronic SCI (cSCI).[3–7] Motor-complete cSCI results in the loss of motor function in addition to autonomic function below the injury site. eSCS has been shown to restore some volitional motor function and to improve autonomic functions, including cardiovascular, sexual, bladder, and bowel functions.[5,6,8,9]

Stimulation of the spinal cord below the level of injury is believed to enable volitional control by recruiting activity of segmental dorsal roots and motor neurons to restore excitatory/inhibitory balance to the spinal segments, allowing residual supraspinal projections to exert influence.[10] Lumbosacral stimulation is performed at the level of the spinal cord corresponding to the motor segments targeted for restoration (approximately T11–L1 spinal levels). Although segmental stimulation appears to provide the possibility of restored function, stimulation typically requires significant voltage or current, which has been shown to affect directly both dorsal roots and the spinal cord.[11] It is not clear whether optimal stimulation to restore function requires targeted stimulation of each segmental circuit or broad, uniform stimulation despite the complex anatomy of the cauda equina and lower nerve roots.[12,13]

Despite its potential for restoring volitional motor control, only specific stimulator electrode configurations enable volitional movement, and these configurations are not always consistent across participants.[5,13] Determining the optimal spatial application of neuromodulation requires using the optimal array of implanted electrodes and optimal intraoperative placement of electrodes to maximize clinical efficacy. All known investigators have used low-frequency stimulation-evoked muscle responses intraoperatively to achieve laterally symmetric stimulation and appropriate rostral-caudal coverage to ensure a minimum engagement of key target muscles.[5,14,15] These evoked muscle responses are measured using electromyography (EMG), which reports the sum of the electrical activity of the muscles beneath or near the EMG bipolar electrodes.

Previous reports of partial restoration of movement after cSCI by eSCS and the consistently reported sensitivity to precise configuration of spatial stimulation highlight competing hypotheses for heterogeneous performance across participants.[5,14,15] Others have shown that stimulation-evoked mapping can target muscles with high anatomic separation and broad stimulation, which can engage all lower extremity muscles used for locomotion.[15,16] It is not clear whether poor performance is due to a lack of supraspinal control relative to other participants (worse injury) or to suboptimal stimulation of the corresponding segmental circuits. Unfortunately, several challenges complicate linking electrode configurations to muscle engagement. First, the complex three-dimensional anatomy of the spinal cord, its movement, and its anatomic variation among patients require complex modeling.[16–18] In addition, stimulation is usually performed using a large paddle lead that provides a limited two-dimensional grid of electrodes.[5,13] Dorsal root ganglion stimulation is an alternative method of neuromodulation with the potential for greater specificity, and preliminary reports indicate that targeted spatiotemporal stimulation at the dorsal roots improves volitional movement after cSCI when extensive optimization is used.[18,19] However, because of the nature of the lumbosacral plexus, nerve roots innervate multiple muscles. Furthermore, the contribution of each nerve root to each muscle can vary among patients.[20] As a result, stimulating dorsal roots or spinal cord segments may not selectively activate muscles in a consistent manner across patients to allow optimal restoration or even target engagement. It is still not known how much control can be exerted through variation in patterns of tonic stimulation as a method of optimization.

To determine the contribution of spatial stimulation to target specific muscle groups using eSCS despite these challenges, we evaluated postoperative stimulation-evoked muscle responses under a wide range of stimulator electrode configurations across several participants. We focused our investigation on three types of stimulator electrode configurations, as illustrated in Figure 1: maximally spatially separable horizontal (same row), vertical (same column), and diagonal (different rows and columns) electrode configurations on a two-dimensional array. We hypothesized that changing the laterality of the dipole resulting from these configurations would enable selective lateral steering of muscle activation biased to the cathode. Given the oblique orientation of spinal roots to the rostral-caudal axis, we predicted that diagonal configuration muscle activation patterns would engage spinal roots that are most proximal and best aligned with the dipole produced by the stimulator. Identifying trends in the evoked muscle potentials associated with these electrode configuration patterns may serve as a first step to enable clinicians to target or adjust stimulation for specific muscle groups using eSCS at therapeutic settings in their patients.

MATERIALS AND METHODS

Participants

Fifteen participants from the Epidural Stimulation After Neurologic Damage trial were included in this study. This study received both local Institutional Review Board and Food and Drug Administration Investigational Device Exemption approval, and its protocol is available at ClinicalTrials.gov (NCT03026816). All participants had complete paraplegia (Abbreviated Injury Scale [AIS] classification A) with injury sites ranging from T3 to T10 (Table 1). At the time of enrollment, the participants were aged 26 to 58 years (average age: 42.5 years), with 1.2 to 16.8 years after injury (average: 6.5 years). Participants included 11 men and four women. The participants provided informed consent and authorization to present information for research purposes. Participants with a chronic, traumatic SCI (of at least one year after injury) were required to be aged > 22 years; to have motor complete AIS classification A or B consisting of a neurological level of injury between C6 and T10; to have complete hand and arm ability and strength; and to have their segmental reflexes intact below the level of injury. More specific details about the study and inclusion/exclusion criteria can be found in previous publications.[5,21]

Implant

Participants underwent implantation of a three-column (5-6-5), 16-contact paddle lead (Fig. 2a) with a primary cell internal pulse generator (Tripole and Proclaim Elite, Abbott, Plano, TX) at approximately the vertebral T11–L1 level, under general anesthesia. Participants 1, 4, and 15 have the paddle oriented in the upright position, whereas the other participants have the paddle inverted

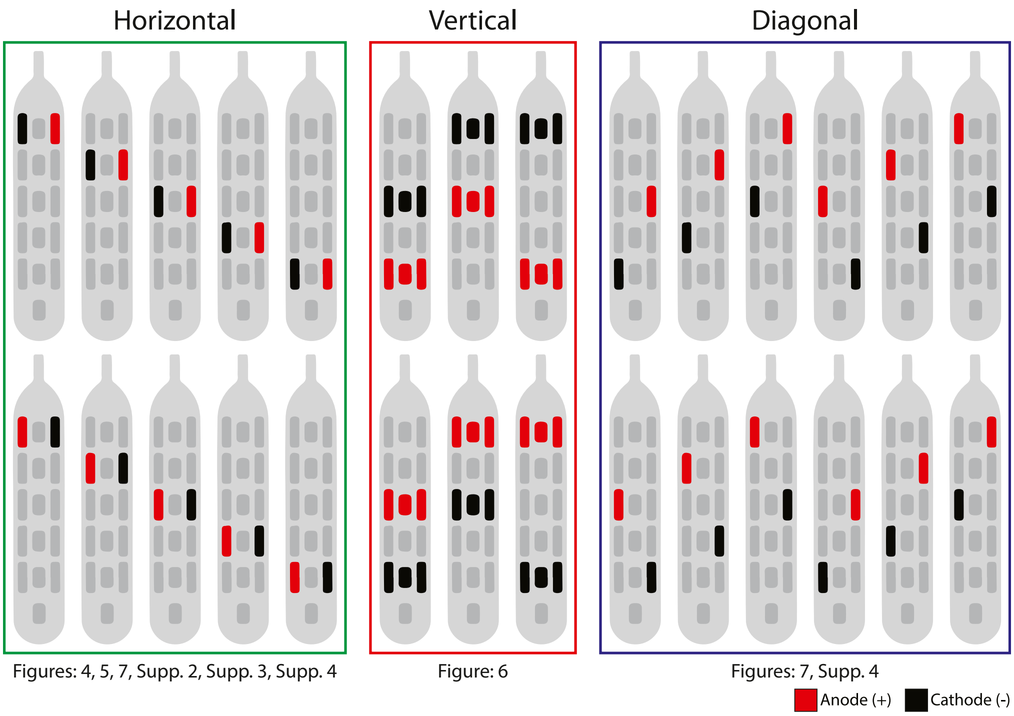

Figure 1. Examples of the electrode configurations that were evaluated. Those in the green rectangle are examples of "horizontal configurations" in which a cathode and an anode are on the left/right sides of a single row on the stimulator. Those in the red rectangle are examples of "vertical configurations" in which there is a row of three cathodes caudal/rostral to a row of three anodes. Those in the blue rectangle are examples of "diagonal configurations" in which a cathode is along a diagonal line with an anode. Each configuration subgroup applies to the figures noted at the bottom of the image. Supp., supplemental. [Color figure can be viewed at www.neuromodulationjournal.org]

(Fig. 2b). Low-frequency (2 Hz, 350–450 μs, 0–10 mA) stimulation-evoked muscle responses allowed electrophysiological mapping to ensure coverage of the lumbar and sacral roots.[14]

The paddle was configured with cathodes inferiorly and anodes superiorly, then shifted intraoperatively until maximal and symmetric muscle recruitment was observed with the most minimal current. Anchors were placed and sutured to secure the paddle, and the wires were tunneled to a subcutaneous pocket in which the pulse generator was secured.

Electromyography

A Natus Nicolet Electrodiagnostic system with an Endeavor 16-channel intraoperative module (Natus Medical Incorporated, Pleasanton, CA) was used for surface EMG recordings. The sample rate for these recordings was 600 Hz. Eight total muscle groups (rectus abdominis [RA], intercostal, paraspinal, iliopsoas, rectus femoris [RF], tibialis anterior [TA], extensor hallucis longus [EHL], and gastrocnemius) on each side were recorded (five in the lower extremities) while the participants lay supine with enough head

Table 1. Demographics and Clinical Features at Baseline.

Participant number	Age range (y)	Sex	Years between injury and surgery	Years between surgery and mapping	Lowest injury site (AIS)
1	50s	F	11.0	0.8	T8 (A)
2	50s	M	1.2	0.2	T3 (A)
3	30s	F	8.2	0.1	T4 (A)
4	70s	M	1.9	0.2	T5 (A)
5	40s	M	16.8	0.7	T8 (A)
6	40s	F	5.4	0.4	T5 (A)
7	50s	M	4.0	1.0	T5 (A)
8	40s	M	5.7	0.3	T10 (A)
9	20s	M	3.1	0.2	T4 (A)
10	40s	M	3.3	0.3	T4 (A)
11	30s	M	8.9	0.4	T4 (A)
12	20s	M	1.6	0.3	T6 (A)
13	30s	M	13.4	0.2	T5 (A)
14	30s	M	10.5	0.2	T8 (A)
15	40s	F	2.1	0.2	T3 (A)

F, female; M, male.

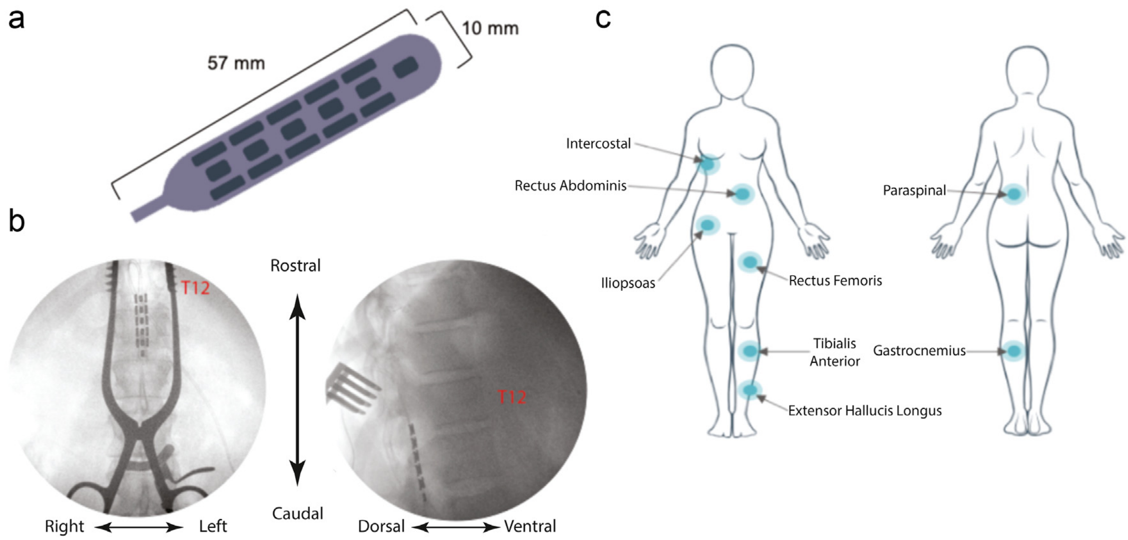

Figure 2. Paddle and EMG lead positioning information. a. Abbott Tripole™ 16-contact lead. Thickness: 2 mm, tapering to 0.4 mm. b. X-ray of implanted lead in participant 7; Left: dorsal coronal view, R, rostral; L, lateral; Right: right sagittal view, R, rostral; D, dorsal. c. EMG lead positions. Blue circles identify muscles and EMG electrode placement for each participant (placed bilaterally). 1. intercostal, 2. RA, 3. iliopsoas, 4. RF, 5. tibialis anterior, 6. extensor hallucis longus, 7. paraspinal, 8. gastrocnemius. [Color figure can be viewed at www.neuromodulationjournal.org]

elevation for them to observe their legs. The EMG electrode locations are depicted in Figure 2c. Electrodes were placed on the T12 paraspinal muscles near the eSCS proclaim paddle implant to detect stimulation artifacts. The surface patch ground was placed 2.5 cm below the umbilicus.

A mapping procedure tested a series of approximately 40 eSCS spatial configurations while holding the stimulation pulse width and frequency constant (300 μs, 2 Hz). Configurations were chosen to evaluate broadly over the spatial space. All combinations of the electrode configurations are shown in Figure 1. The diagonal configurations were not applied to participants 1 and 6 owing to early changes in study protocol. Participant 6 also did not have vertical configurations tested because of missing data. For each setting, the current was increased at an average rate of 0.4 mA step size until the participant exhibited a constant muscle twitch, defined as a rhythmic muscle contraction that was involuntary and persisted if the current was maintained. This current level was then held for 5 to 10 seconds before the current was again increased at an average step size of 0.4 mA until the RF, TA, EHL, and gastrocnemius muscle groups exhibited a visible muscle twitch.

All tested electrode configurations were bipolar and included configurations parallel, perpendicular, and diagonal relative to the lead length. In addition, the mapping procedure for each participant was conducted in a single visit, taking an average of one hour per session. The participants were placed in the supine position and were not moved during each stimulation setting.

Signal Processing

For each participant, EMG data were isolated for both a baseline period during which no stimulation was administered and trial periods corresponding to the first 5 seconds after each of the electrode configurations being tested was applied. An ideal high-pass filter at 1.5 Hz and an ideal notch-filter for 59–61 Hz were applied by filtering in Fourier space. We defined the metric of activation in each muscle to be the stimulation-evoked muscle potential (EMP) amplitude. To calculate the baseline noise on each of the 16 channels (one for each muscle group, bilaterally), 30 random 30-millisecond EMG samples were taken during the 4 minutes before the start of stimulation, computed using the “randi” function in MATLAB (MathWorks, Natick, MA). The average peak-to-peak EMG amplitude across these samples was used to calculate the baseline potential amplitude for each muscle group. These amplitudes were subtracted from the trial evoked potential amplitudes.

The timing of trial EMPs was isolated for each electrode configuration by determining which EMG channel displayed the greatest range in potential in the first 5 seconds after the configuration was applied. The time of this peak-to-peak amplitude indicated when the EMP began. The peak-to-peak potential was calculated on each channel within 15 milliseconds before and after this maximum peak. These values were averaged across the nine pulses in the 5-second window of data. Baseline values were subtracted from the average, and any negative values were set to zero. To compare across participants, each participant's results for each muscle were normalized to the maximum EMP value on that muscle for any setting for that participant's session.

Statistics

MATLAB (Release 2021a) software was used for statistical analyses. For each horizontal electrode configuration and muscle group, the measured activation of the right side of the given muscle group was subtracted from that of the left side of the given muscle group to yield a skew value. These activation skew distributions were evaluated using Wilcoxon signed-rank tests—one test per muscle and paired by participant. The test determined whether the difference between medians with the cathode position on the right or left side of the participant's body was significantly greater than or less than zero.

For vertical electrode configurations, the measured activation of each muscle group when the row of cathodes was rostral to the row of anodes was subtracted from measured activation when the row of cathodes was caudal to the row of anodes. The resulting skew value distributions for each muscle group were then evaluated using a Wilcoxon signed-rank test to determine whether their medians were significantly greater than zero.

For diagonal electrode configurations, for each muscle and participant, we computed the activation of the muscle with a horizontal configuration and subtracted this value from the muscle activation resulting from the diagonal configuration(s) that had their cathode in the same position as this horizontal configuration. These difference values were then compiled across all participants into boxplots for each muscle group, and a Wilcoxon signed-rank test was performed to determine whether the median difference in muscle activation was significantly greater than zero for each of these muscle groups.

For the analyses of the horizontal, vertical, and diagonal electrode configurations, skew values were excluded when both muscle activation values used to calculate the skew value were < 5% of the maximum activation in that muscle group and participant.

RESULTS

Twitch Amplitudes

Visual review of a small number of random trials showed that time windows around EMPs were effectively isolated on EMG, as shown by the arrows in Figure 3. Summarizing the muscle activation for each configuration showed that the response varied greatly across configurations and participants. Left and right example horizontal configurations for participant 10 shown in Figure 3 are representative of the variation between similar configurations. Supplementary Data Figure S1 shows another horizontal-to-diagonal within-participant comparison.

Spatial and Orientation Dependence

Exact *p* values for the following figures are in Supplementary Data Table S1. Bipolar configurations were selected to be tested in three broad classes: horizontal configurations (Figs. 4 and 5), vertical configurations (Fig. 6), and diagonal configurations (Fig. 7 and Supplementary Data Figure S2). When horizontal configurations were used, we found that muscles were more activated on the side of the body ipsilateral to the cathode. When combining the data across 15 participants, this skew was statistically significant ($p < 0.05$) for 12 of the 16 muscles tested. In addition, when combining data, all eight muscle groups tested for each side (for a total of 16 muscles as previously shown in Fig. 2c) indicated a significant difference ($p < 0.05$) in muscle skew among the cases in which the cathode was on the left and when it was on the right. However, the skew data for individual participants showed significant variation in the number of muscle groups/distributions that showed statistical significance, as shown by two representative participants in Figure 5. Data visualization for all 15 participants is shown in Supplementary Data Figures S3 and S4.

Only two of the eight muscle groups tested (the RF and EHL) showed significantly ($p < 0.05$) more activation when the row of cathodes was caudal to the row of anodes than when the row of cathodes was rostral to the row of anodes in the vertical configurations, as shown in Figure 6. In this figure, data for both sides of each muscle group were combined in each muscle group category to isolate the influence of spinal nerve root level on differential muscle group activation vertical configuration orientations. The observation that when the vertical configuration data for all muscle groups and patients were pooled together, caudal cathodic stimulation resulted in significantly greater muscle activation is likely due to the large number of samples in this group (672) and is not clinically meaningful because the difference in muscle activation relative to the opposite configuration was very close to zero.

Pooling data across the 13 participants, we observed significantly ($p < 0.05$) greater activation in the RA, intercostal, paraspinal, iliopsoas, and TA muscles when diagonal configurations were used than when the horizontal analogs were used, as shown in Figure 7. Supplementary Data Figure S2 provides heatmaps to elaborate the comparisons between diagonal and horizontal configurations for

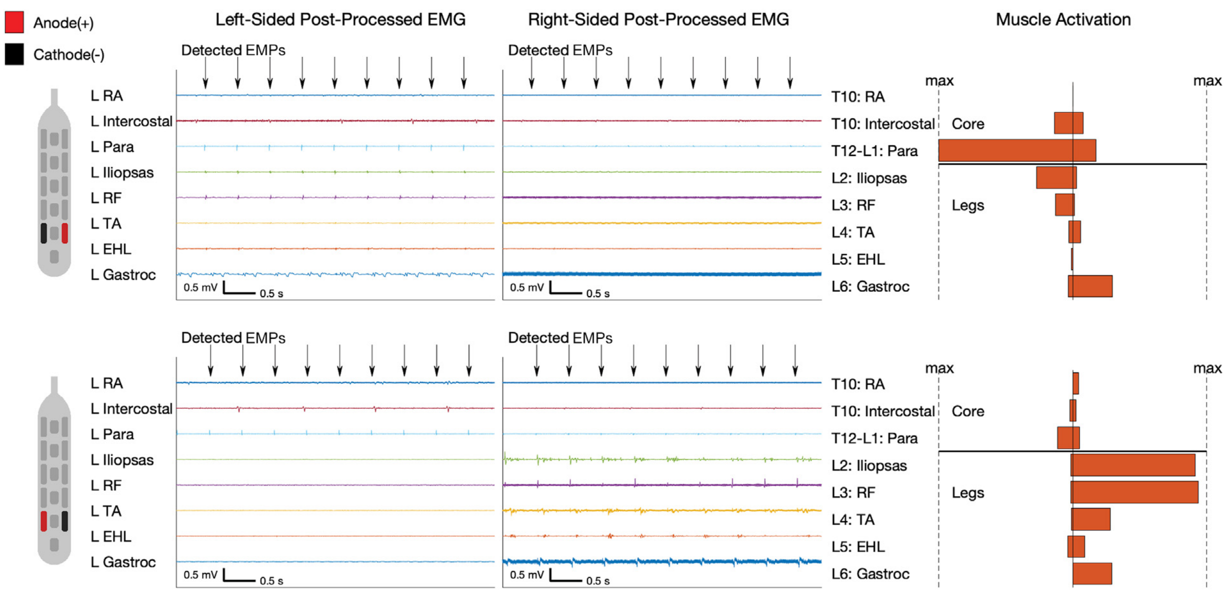

Figure 3. Muscle activation calculation on the left and right for participant 10 comparing left and right horizontal anode configurations. EMPs are detected from processed EMG using different channels. Average EMG amplitudes for each configuration and muscle group are normalized to the maximum across each muscle group during the day and plotted to show that the response varies with electrode configuration. max, maximum; EMPs, evoked muscle potentials. [Color figure can be viewed at www.neuromodulationjournal.org]

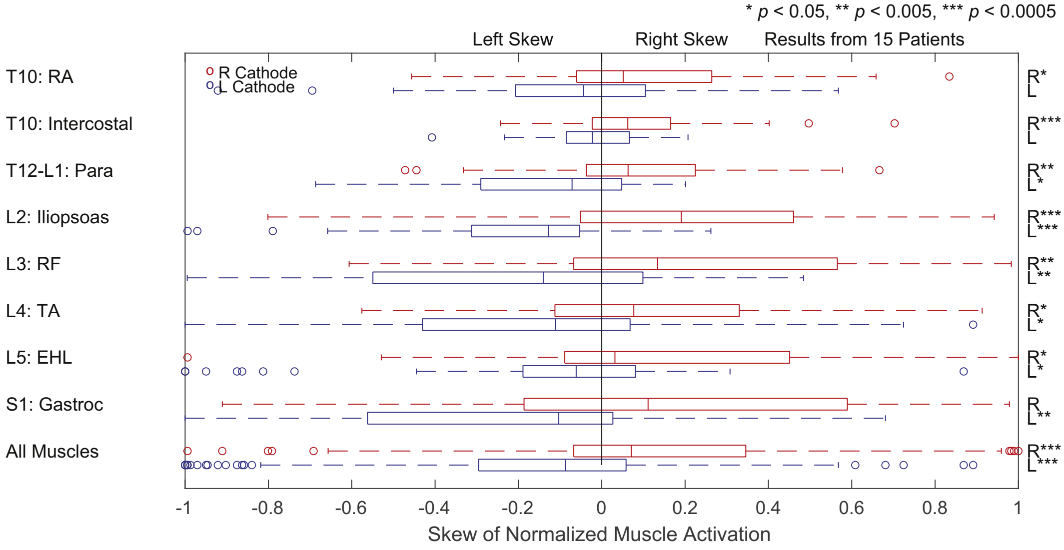

Figure 4. Horizontal configuration results across all participants with Wilcoxon signed-rank significance testing. Twelve of the 16 distributions showed a significant skew in the direction ipsilateral to the cathode. [Color figure can be viewed at www.neuromodulationjournal.org]

each muscle group on each side. We observed that for the left and right RA, left and right paraspinal, and left intercostal muscles, all diagonal configurations had significantly ($p < 0.05$) greater muscle activation than did the analogous horizontal configurations. In addition, for each of the right iliopsoas and left iliopsoas, only one diagonal configuration type did not have significantly greater muscle activation than that of its analogous horizontal configuration type.

DISCUSSION

The need to personalize and adapt eSCS to restore function after cSCI spawned our efforts to evaluate the specificity of stimulation-evoked responses across a broad range of patterns of stimulation to elicit specific changes in evoked responses after surgery. We found 1) significant specificity in laterality of muscle activation with cathodic stimulation using horizontal configurations, 2) minimal variation of muscle group activation with vertical variation in stimulation, and 3) some improvements in evoked activity with diagonal stimulation over horizontal.

Electrode Configuration-Related Muscle Activation Trends

Horizontal Configuration

These results reveal a statistically significant difference in the muscle activation pattern between cathodes in a horizontal spatial pattern on the right side of the electrode from when they were on the left side of the electrode (in the participant's frame of reference). The results in Figure 4 indicate that for 12 of the 16 muscles tested, there was significantly more muscle activation when the cathode was ipsilateral to that muscle than when it was contralateral to that muscle. On the other hand, the box plots in Figures 4 and 5 indicate that some participants displayed more activation when the cathode was contralateral to that muscle. The muscle activation skew data for individual participants in Figure 6 and in the Supplementary Data figures also show variability in the muscle activation skews between participants, meaning that each person's response to a directional transverse stimulation vector is, in part, idiosyncratic. The ability to selectively steer muscle activation laterally over a patient's body is a desirable characteristic when optimizing electrode configurations because it may allow resolution of any asymmetries in muscle activation. Ipsilateral selectivity of stimulation has previously been established in multiple models using the strategy of offsetting bipolar stimulation to the left or right, amplifying ipsilateral movement in animal[22] and computational[16,18] models. Our approach steers current across the transverse cord, which is similar to one tactic used by a recent computational model validated intraoperatively, although their approach tested multipolarity and lateral positioning instead of whole transverse dipole.[18] Steering current longitudinally down lateral tracts vs steering a current to the left and right across all tracts are fundamentally different approaches, meaning that indication of lateral selectivity using each method is informative of the underlying mechanism guiding optimal side-specific stimulation. Overall, these results indicate that if a clinician is attempting to stimulate muscles on a particular side of a patient's body, an effective starting point may be to steer the cathodes in the spatial pattern they are using toward the side of the stimulator that is ipsilateral to those muscles with an understanding that there is significant variation in response.

Vertical Configuration

Varying cathode location along the rostral-caudal axis produced a less distinct effect than was seen with the horizontal configurations. The results depicted in Figure 6 indicate that only two muscles (the RF and EHL) displayed significantly greater activation than did the opposite case when the row of cathodes in the electrode configuration was rostral to the row of anodes. This may be because the segment of the spinal cord or nerve root innervating these particular muscles intersects better with the dipole filtering through the dura.[23] Thus, whether the row of cathodes is rostral or caudal relative to the row of anodes may more significantly affect muscles whose nerve roots derive from spinal cord segments and dorsal roots that overlap with the dipole generated by the paddle than other muscles with nerve roots that derive from other segments of the spinal cord. The

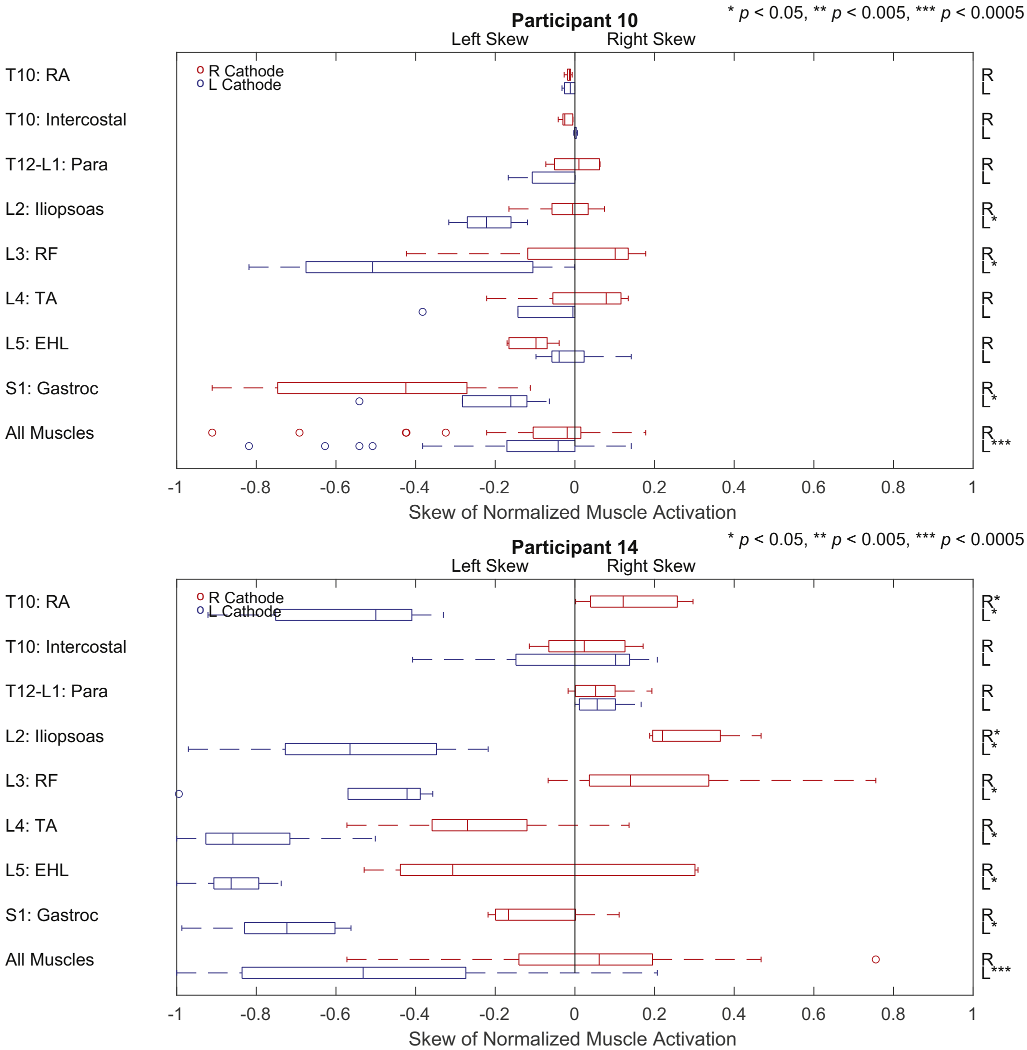

Figure 5. Horizontal configuration example results for two individual participants (10 and 14) with the Wilcoxon signed-rank test for the distributions depicted. For participant 10, three muscle group distributions showed a significant difference in the median activation skew when the cathode was on the left side of the stimulator, which was ipsilateral to the left-sided cathode. For participant 14, eight of the 16 distributions indicated a significant activation skew in favor of the muscles on the side of the participant's body ipsilateral to the cathode. [Color figure can be viewed at www.neuromodulationjournal.org]

muted effect of the direction of rostral-caudal stimulation compared with previous studies can be explained by differences in design: a previous study showed differential activation of particular muscles based on rostral-caudal stimulation changed both the position of the cathodes and polarity of the steered vector simultaneously,[15,16] whereas this study accounted for each pattern change separately and with consideration of a slightly different assortment of muscles. In addition, a modeling study showed that the stimulation voltage threshold for muscle excitation for the L4 section of the spinal cord (which significantly contributes to the innervation of the RF) was lower when a cathode was rostral relative to the anode, which is consistent with our findings.[23] In contrast to the horizontal configurations, the vertical configuration data for individual participants were not analyzed separately (Figure 6 included data for all the participants) because of limited power. We do not have strong recommendations for using vertical configuration strategies to elicit responses in more rostral or caudal lower extremity muscles at a group level beyond a couple of muscles with likely a maximum of anatomic separation, which agrees with previous reports.[16]

Diagonal Configuration

Evaluating diagonal electrode configurations enabled us to explore the effects of dipoles that were oblique to the rostral-caudal axis. Given that spinal roots are oblique to the rostral-caudal axis, we anticipated that the muscle stimulation pattern for a given diagonal configuration may correlate with the spinal roots that are closest to and best aligned with the corresponding dipole, as suggested in previous computational models.[16,18] However, this was not the case. The results depicted in Figure 7 and Supplementary Data Figure S2 indicate that for 30 of the 32 configuration pairs tested, the RA, intercostal, paraspinal, and iliopsoas muscle groups, diagonal configurations produced significantly ($p < 0.050$) greater muscle activation than did the analogous horizontal configurations. These results were regardless of whether the anode in the diagonal configuration was caudal or rostral relative to the cathode, suggesting that the reason for the greater effectiveness of diagonal configurations relative to horizontal configurations is not necessarily because of their greater alignment with the nerve roots coming off the spinal cord. Their greater

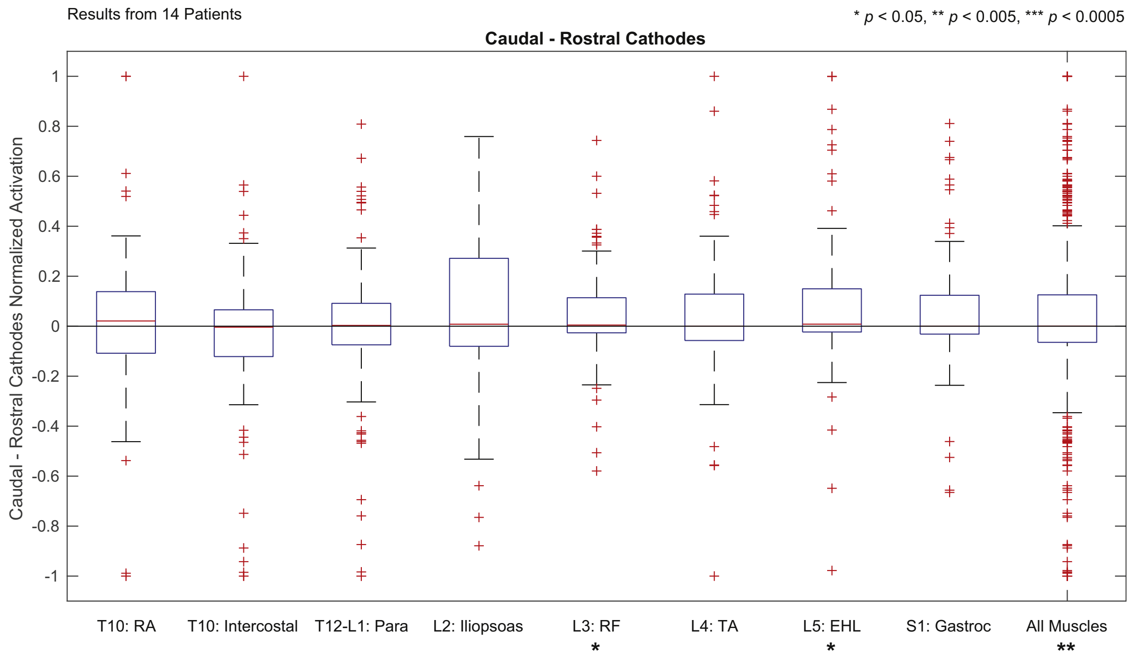

Figure 6. Vertical configuration results across 14 participants. When the vertical configuration skew data for all the participants were combined, the results from a Wilcoxon signed-rank test indicated that the only muscle groups that showed significantly greater activation when the cathode row was caudal to the anode row (relative to when the cathode row was rostral to the cathode row) were the rectus femoris and extensor hallucis longus muscle groups. [Color figure can be viewed at www.neuromodulationjournal.org]

effectiveness may be explained by the fact that the dipole produced by diagonal configurations spreads over more of the spinal cord than that produced by horizontal configurations. This is consistent with earlier computational and experimental models that show dissemination of the extracellular current around the cerebrospinal fluid away from the initial stimulation vector, distributing the area of effect.[22] To apply these findings clinically, when a physician is attempting to more broadly activate the RA,

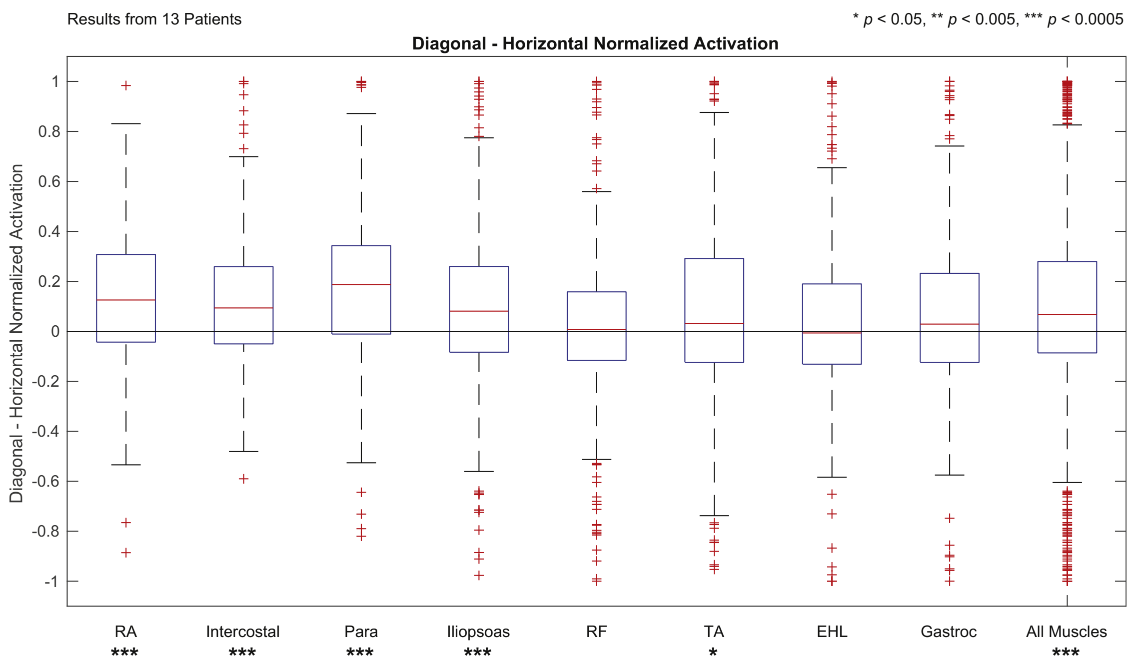

Figure 7. Comparison of diagonal and horizontal configuration activation values across 13 patients. When the diagonal vs horizontal configuration data for all participants were combined, the results from a Wilcoxon signed-rank test indicated that all muscle groups tested, except the rectus femoris, extensor hallucis longus, and gastrocnemius muscle groups, indicated significantly (at least $p < 0.05$) greater muscle activation with a diagonal electrode configuration than with a horizontal electrode configuration. [Color figure can be viewed at www.neuromodulationjournal.org]

intercostal, paraspinal, and iliopsoas muscle groups, they may consider including diagonal electrode configurations.

Necessity of Patient-Specific Empirically Informed Programming

The observed relations described here warrant further investigation into the predictive value of evoked muscle potentials for functional outcomes for patients with eSCS. Given the variability observed among patients, these relations also suggest they may best serve as initial starting points for clinicians or researchers as they attempt to target specific muscle groups, with EMG measurements being used for fine-tuning and verification that the observed relations hold for individual patients, as others have already used.[18] More personalized targeting could be achieved through specifically designed paddle electrodes and/or direct dorsal root ganglion stimulation as reported by others.[19]

Limitations

A limitation of this study is that the set of possible stimulator electrode positions relative to each participant's spinal cord was constrained by the initial surgical placement of the stimulator. Although the surgical process is the same, anatomic variation likely introduces some differences. Also contributing to the observed variability may be the fact that the exact stimulation amplitude a participant received was nonlinearly related to the observed muscle activation, which is necessary owing to anatomic variation. The possibility of lead migration of the paddle is a known complication that introduces random error among participants and sessions. This is limited by securing the paddle with anchors during the implantation procedure. Furthermore, normalization was a challenge in this study. Although each of the muscle activation data from a given muscle group were normalized by dividing the raw activation values by the maximum activation observed in that muscle group and participant, there is no guarantee that this divisor was truly the maximum activation value possible from that muscle. Lastly, this study remains cross-sectional in nature, and others have shown some variation in time.[14] Future work should investigate the stability and reliability of stimulation-evoked responses across longer periods.

CONCLUSIONS

Spinal cord stimulation delivered through an epidural paddle produces evoked responses across muscle groups in a manner highly dependent on the stimulator electrode configuration. Although we observed significant variation between individuals, cathodic stimulation can be used to improve the laterality of targeted muscles and when used at an angle, can improve overall recruitment. Despite being the largest programmable maneuver, moving cathodes vertically across the paddle can only improve recruitment of a minority of muscles. Most importantly, the significant interpatient variability in evoked muscle response observed for similar electrode configurations necessitates procedural mapping be performed for each patient, even if many more such relations are identified.

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Authorship Statements

David P. Darrow, Theoden I. Netoff, Uzma Samadani, Ann Parr, and David Balser contributed to the design of the Epidural Stimulation After Neurologic Damage (E-STAND) study. David P. Darrow, Theoden I. Netoff, and Matthew D. Johnson designed this mapping study for the E-STAND trial. David P. Darrow, Caleb Hoover, and David Balser recruited participants and collected most of the study data. Under the supervision of David P. Darrow, Theoden I. Netoff, and Matthew D. Johnson, Julia P. Slopsema, Lauren R. Madden, Claire A. Zurn, and Brandon K. Hoglund completed the processing pipeline and statistical analysis and created the data visualizations for the study. Brandon K. Hoglund, David Balser, Theoden I. Netoff, and David P. Darrow prepared the manuscript draft and reviewer responses. All authors approved the final manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.10.058.

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COMMENTS

In this article, Hoglund et al map the effects of eSCS on evoked muscle responses in study participants with chronic SCI. Recent developments using eSCS have shown exciting results indicating the restoration of motor function within individuals with chronic SCI. However, previous studies mostly consisted of small study populations and case series, which may not translate to wider populations as SCI is a very heterogeneous disease. Therefore, one reason eSCS has yet to translate to clinical practice is due to a lack of clear guidelines regarding optimal stimulation parameters that can be utilized across a wide study population. The work presented here represents the first step toward establishing guidelines on electrode configurations used to target muscle recruitment in a clinical population and represents a significant step forward in the number of study participants included in an eSCS study. Although there are many steps remaining prior to clinical translation of this exciting technology, the data shown here will provide baseline knowledge to scientists and researchers as the field of eSCS continues to expand.

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