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Effects of paired transcutaneous electrical stimulation delivered at single and dual sites over lumbosacral spinal cord

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Abstract

It was demonstrated previously that transcutaneous electrical stimulation of multiple sites over the spinal cord is more effective in inducing robust locomotor behavior as compared to the stimulation of single sites alone in both animal and human models. To explore the effects and mechanisms of interactions during multi-site spinal cord stimulation we delivered transcutaneous electrical stimulation to the single or dual locations over the spinal cord corresponding to approximately L2 and S1 segments. Spinally evoked motor potentials in the leg muscles were investigated using single and paired pulses of 1 ms duration with conditioning-test intervals (CTIs) of 5 and 50 ms. We observed considerable post-stimulation modulatory effects which depended on CTIs, as well as on whether the paired stimuli were delivered at a single or dual locations, the rostro-caudal relation between the conditioning and test stimuli, and on the muscle studied. At CTI-5, the paired stimulation delivered at single locations (L2 or S1) provided strong inhibitory effects, evidenced by the attenuation of the compound responses as compared with responses from either single site. In contrast, during L2-S1 paradigm, the compound responses were potentiated. At CTI-50, the magnitude of inhibition did not differ among paired stimulation paradigms. Our results suggest that electrical stimuli delivered to dual sites over the lumbosacral enlargement in rostral-to-caudal order, may recruit different populations of motor neurons initially through projecting sensory and intraspinal connections and then directly, resulting in potentiation of the compound spinally evoked motor potentials. The interactive and synergistic effects indicate multi-segmental

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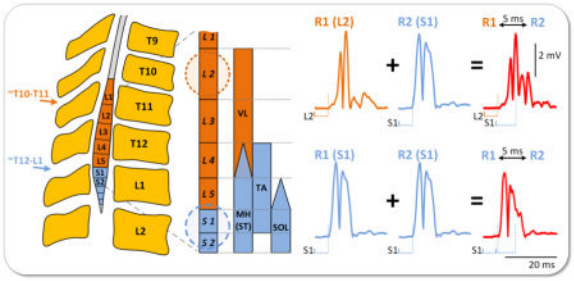
convergence of descending and ascending influences on the neuronal circuitries during electrical spinal cord stimulation.

GRAPHICAL ABSTRACT



Keywords

human; transcutaneous spinal cord stimulation; spinally evoked motor potentials; electrophysiological assessment; neurorehabilitation

Introduction

Studies in animals have shown that electrical stimulation of the more rostral segments of the lumbar enlargement is critical for the initiation of stepping movements [2, 17]. It has been further demonstrated that epidural stimulation in the presence of serotonin agonists applied independently at the L2 and S1 spinal cord segments facilitated full weight-bearing stepping in rats with a complete mid-thoracic spinal cord transection [6, 20]. In addition, site-specific effects of spinal cord stimulation were reported: Upper lumbar stimulation engaged the neural circuits controlling flexion, whereas upper sacral stimulation primarily recruited the circuits controlling extension during stepping [6]. These data are consistent with the presentation that the lumbosacral enlargement not only contains motor neuron pools projecting to proximal and distal leg muscles, but also encompasses neuronal networks controlling locomotion and standing [9, 11]. In human, it has been reported that epidural stimulation of the spinal rostral segments (L2) is more effective for inducing rhythmic movements [10], whereas stimulation of more caudal segments (S1-S2) allows for greater postural control [12]. These observations are suggestive of the possibility that stimulation of multiple spinal sites related to postural and locomotor circuitries activation might be complementary in inducing the most effective coordinated stepping-like as well as postural movements. Most recently, we have reported that dual-site transcutaneous electrical stimulation delivered above T11 and L1 vertebrae is more effective in inducing robust locomotor behavior as compared to the stimulation of each site alone in non-injured individuals [11]. We demonstrated that although the stimulation was delivered with the same frequency of 30 Hz, the observed induced “pace” of the step-like movements differed between the three paradigms: with lower frequency of movements during stimulation delivered over T10, higher frequency during stimulation delivered over L1, and larger excursion of the flexion-extension movements and a mixed EMG pattern during dual-site stimulation [11].

At the same time, the mechanisms mediating the effects of interactions during spinal cord stimulation at multiple sites have not been explored yet. We recently demonstrated that transcutaneous electrical spinal cord stimulation can be used to differentially activate dorsal roots and corresponding motor pools based on their anatomical arrangements along the rostro-caudal axis of the lumbosacral enlargement [25]. In light of the spatial arrangement of the motor pools and networks along the lumbosacral enlargement (Fig. 1A), it seems plausible to hypothesize that electrical stimuli delivered to multiple sites over the lumbosacral enlargement can recruit different populations of motor neurons inside the same motor pool, as well as activate different combinations of networks. To test our hypothesis, we developed surface electrode array to investigate the modulatory effects of the paired spinal cord stimulation delivered to the single or dual locations with different delays on spinally evoked motor potentials in the leg muscles. We suggested that depending on the spatiotemporal characteristics of the paired stimulation delivery, the effects can be complementary or competitive.

Methods

Experiments were conducted in 6 volunteers (4 males and 2 females; mean ± SD: age 28.7 ± 3.8 yrs, height 171.7 ± 11.8 cm, body mass 74.8 ± 14.4 kg). None of the participants had any history of neurological or orthopedic disorders. Participants provided written informed consent to the experimental procedures, which were approved by the local institutional review board. Detailed description of the transcutaneous electrical spinal cord stimulation protocol has been reported [25]. During the experiment, the participants stayed relaxed in a supine position. A custom-built constant current stimulator was used to deliver the stimulation which was administered through a 9-electrode array placed on the skin at the midline between the spinous processes of the T10 and L1 vertebrae as cathodes, and two 5 × 9 cm self-adhesive electrodes (Pro-Patch, Taiwan) located symmetrically on the skin over the iliac crests as anodes. The 9-electrode array consisted of 3 rows and 3 columns of silver-silver chloride cup electrodes (10 mm of diameter), spaced approximately 15 mm apart (center-to-center). The midline electrodes from the top and bottom rows were used during the experiment. We positioned the electrode array such that at more rostral stimulation levels (~L2 spinal segment), the threshold was lower for the proximal pools, whereas at more caudal stimulation levels (~S1 spinal segment), the threshold was lower for the distal pools [25]. This ensured that stimulation locations were similar with respect to position of the lumbosacral spinal cord in all subjects [25, 29].

Surface electromyogram (EMG) signals were recorded bilaterally using bipolar surface electrodes (Motion Lab Systems, Baton Rouge, LA, USA) placed longitudinally on the soleus (SOL), tibialis anterior (TA), vastus lateralis (VL), and medial hamstrings (MH) muscles with fixed inter-electrode distance of 17 mm. The EMG signals were differentially amplified with a band-pass filter of 10 Hz to 2 kHz (−3 dB), and digitized at a sampling rate of 5000 Hz.

The digitized EMG time series were full-wave rectified after subtraction of the mean background EMG.

First, stimulation was delivered as single 1 ms, monophasic, square-wave pulses every 6 s. Recruitment curves were constructed by plotting the magnitude of spinally evoked potentials against increasing stimulation intensity at each and both stimulation locations (Fig. 1B). To assess the modulatory effects of paired spinal stimulation single control stimuli were delivered at each stimulation location at an intensity corresponding to 10–50% of maximum response magnitude. This was followed by paired pulse stimulation, administered at conditioning-test intervals (CTIs) of 5 and 50 ms, at single and dual spinal levels using the following paradigms: L2-L2, S1-S1, S1-L2, and L2-S1. In 4 out of 6 participants, the CTIs were additionally administered at 10, 25, 75, and 100 ms. Only CTIs of 5 and 50 ms were analyzed. Stimulation intensities that produced smaller responses were chosen in order to minimize the spread of current to adjacent spinal segments, as well as to ensure predominantly afferent fibers' activation [24]. During the S1-L2 and L2-S1 paradigms, the stimulation intensities were adjusted such that the magnitude of single responses in different muscles at a given level matched those at other level (Figs. 1B and 2). A minimum of 3 stimuli were delivered at each condition.

Magnitudes of the spinally evoked potentials were calculated by measuring the area under the curve within the time windows varying for different muscles between 20 to 40 ms [25]. Paired spinally evoked motor potentials 50-ms apart (CTI-50) were identified and categorized as the conditioning (R1) and test (R2) responses in order to investigate the neural mechanism of post-stimulation modulation [16, 22, 24]. To quantify post-stimulation modulation of the responses, the inhibition ratio was calculated by dividing the magnitude of R2 by R1. A ratio of 1.0 indicated that no post-stimulation modulation occurred; whereas a ratio of 0 indicated the greatest attenuation, such that R2 was entirely abolished.

In 5-ms paired responses (CTI-5), the brief stimulus interval resulted in an R1 response superimposed on the R2 response (Fig. 3). Therefore, the R2 response magnitude was calculated by subtracting the R1 magnitude from the compound R1+R2 magnitude. The post-stimulation modulation was then calculated by dividing the magnitude of R2 by the R1. Positive values indicated that the compound R1+R2 response was larger than the R1, whereas negative values indicated that the compound response was smaller than the R1 (Fig. 3).

The post-stimulation modulation ratio for each muscle was submitted to a 4 stimulation locations by 2 CTIs analysis of variance (ANOVA). A post-hoc t-tests with Bonferroni correction were made to decompose any significant effects ($\alpha = 0.05$). In order to account the number of comparisons the alpha value was corrected to 0.008 ($\alpha = 0.05/6$). The pooled results are summarized in boxplots with the box as the 25–75th percentile, and the whiskers as the highest and lowest values.

Results

Figure 3 presents averaged SOL responses in one participant during paired stimulation delivered during S1-S1 (top row) and L2-S1 (bottom row) paradigms. When both the conditioning and test stimuli arrived at a single location (S1-S1) at shorter CTIs, R1 and R2 responses were superimposed on each other, such that it was impossible to distinguish one

from another; whereas, during L2-S1 paradigm, the compound R1+R2 response had larger magnitude as compared with the control single responses, and included both R1 and R2 waveforms. Fig. 3 presents CTI-5 and CTI-10 for visual comparison to indicate the abolishment of the R2 during S1-S1 paradigm, and R2 appearance and temporal shift of its onset, during L2-S1 paradigm. At CTI-50, the R2 was completely abolished during L1-L1 paradigm, and still present although attenuated at L2-S1 paradigm.

Figure 4 demonstrates the pooled data on the amount of post-stimulation modulation occurred when the paired stimulation was delivered with at CTI-5 and CTI-50 at various spinal levels. The analysis yielded significant effects for the CTIs in VL and MH ($F_{2,5} > 6.62$, $p < 0.05$), stimulation location in all muscles ($F_{4,5} > 7.33$, $p < 0.001$), as well as the interaction between CTIs and stimulation location in each muscle studied ($F_{6,5} > 5.36$, $p < 0.003$). At CTI-5, the paired stimulation delivered at single locations (L2-L2 and S1-S1) provided strong inhibitory effects, evidenced by the attenuation of the compound responses as compared with responses from either single site. The conditioning R1 stimulus arriving at the caudal location (S1-L2) caused similar inhibitory effects on R2 in more caudally located TA and SOL, as opposed to MH and VL. During L2-S1 paradigm, the compound responses were potentiated in all muscles, although the R2 values were in general below 1.0, indicating that the test response was inhibited after the subtraction of the conditioning one. The difference in the post-stimulation modulation during L2-S1 paradigm as compared with other ones, increased in more caudally located motor neuron pools. At CTI-50, the magnitude of R2 inhibition did not differ among paired stimulation paradigms.

Discussion

The magnitude of the response to a second stimulus depended on CTIs, whether the paired stimuli were delivered at the single or dual locations, the rostro-caudal levels of the stimulation delivery, and on the muscle studied.

Paired spinal cord stimulation with CTI of 50 ms has been used previously to investigate and confirm the reflex origin of the spinally evoked motor potentials in non-injured individuals [7, 13, 19, 24, 29]. Such tests were made on the assumption that the long recovery cycle of spinal monosynaptic reflex [27] will result in the disappearance of the indirect component in the second response, leaving the direct one unchanged, since after 50 ms nerve fiber excitability is fully restored. We used different CTIs based on the different mechanisms suggested to contribute to the post-stimulation modulation, which include recurrent inhibition at CTIs less than 10 ms, as well as homosynaptic (post-activation) depression, and modulation mediated through homonymous and heteronymous circuits [22]. Contribution of recurrent inhibition at shorter CTIs may explain stronger inhibitory post-stimulation effects at CTI-5 during L2-L2, S1-S1, and S1-L2 paradigms as compared with CTI-50. During L2-S1 paradigm, the paired stimulation delivered at CTI-5 had rather complementary effects on the compound response, and resulted in its potentiation, and less depression of the R2 as compared with CTI-50.

We suggest that our findings should be considered in light of the topographical characteristic of the lumbosacral cord organization, including anatomical arrangement of the motor pools

and their innervation along the lumbosacral enlargement [1, 15], the average length of the corresponding spinal segments [26], as well as the density of limb motor neurons in the spinal segments [28]. Indicated in Figure 1A, the VL motor pool extends between L2 and L4 segments, whereas more distal SOL, TA, and MH motor pools are condensed in shorter L4 and S2 segments. This can explain why more pronounced post-stimulation effects were observed in more focused motor pools of SOL, TA, and MH, as compared to relatively little changes in extended VL motor pools at corresponding CTIs and paradigms (Fig. 3–4): With various stimulation paradigms, different amount of projecting sensory fibers and different populations of motor neurons can be activated within given motor pools. Another plausible explanation for these differences should account the variation in diameter and number of low-threshold Ia afferents projecting to specific motor neuron pools, as well as to the type and size of the motor neurons [22, 25]. For instance, SOL and MH have larger diameter Ia afferents, as compared to the VL [18, 22], suggesting the larger amount of Ia–α-MN synapses being used, and, as such, their higher sensitivity to post-synaptic inhibition, especially considering our low stimulation intensities.

During the 5-ms apart stimulation, we observed quite contrasting post-stimulation modulatory effects especially of the caudal motor pools with the compound responses being potentiated during L2-S1 and mitigated during L2-L2, S1-S1, and S1-L2 (except of VL) paradigms. It suggests that the order of the motor pools activation was different in these paradigms: During the L2-S1 paradigm, the conditioning stimulus activates certain amount of motor neurons within a pool and interneuronal circuits indirectly through projecting sensory fibers and heteronomous connections from adjacent spinal segments, whereas the test stimulus arrives to the rest of motor pool and results in the potentiated effects. On contrary, during the S1-L2 paradigm (and similar to the single site L2 and S1 paired stimulation), the conditioning stimulus activates the considerable portion of the motor pools below the stimulating electrodes, and causes inhibitory effects through recurrent mechanism onto the test stimulus. These results correspond with the topographical organization of the lumbosacral motor pools described above, and concur with the evidence on the heteronymous connections between the motor pools. In humans, heteronymous monosynaptic Ia projections were demonstrated from quadriceps to soleus, using the-H reflex method [3]. Stimulation of the femoral nerve facilitates the soleus H-reflex, and this appears at low threshold, consistent with a group Ia effect. As such, spinally evoked motor potentials can include the sum effects of all the Ia-sensory volleys conveyed from a number of afferents to given motor neuron pools. In addition, it seems feasible that that the corticospinal tract may be activated through lateral or dorsal columns passing between L2 and S1, thus resulting in the conditioning effects during L2-S1 paradigm. As it was demonstrated earlier [14], corticospinal axons make monosynaptic connections with lower extremity motor neurons in humans [4], however it is unlikely that these fibers contribute to the L2-S1 post-stimulation conditioning observed in our study for the following reasons. First, these axons are located in the dorsal and ventral parts of the lateral column [21] and would require more current than the smaller but more superficial dorsal column fibers [5]. Computational models of epidural or transcutaneous spinal cord stimulation over the lumbosacral cord demonstrated that Ia afferents in dorsal root fibers have significantly lower excitation thresholds compared with dorsal column fibers [23], with the latter requiring

triple the stimulation intensity [8]. Although it is difficult to test, at the low-to-medium stimulation intensity levels used in our study, it seems unlikely that the current would "penetrate" to the neural structures located at the lateral and dorsal columns. We suggest that the most pronounced differences in the post-stimulation modulatory effects across different stimulation paradigms observed at shorter CTI should warrant further research towards its application in functional rehabilitation.

Conclusion

The present findings further demonstrate that transcutaneous electrical spinal cord stimulation can be used to differentially activate selective motor pools via projecting dorsal roots, and induce modulatory effects depending on the spatiotemporal stimulation characteristics. Electrical stimuli delivered to dual sites over the lumbosacral enlargement in rostral-to-caudal, but not in caudal-to-rostral, orders, may recruit different populations of motor neurons initially through projecting sensory and intraspinal connections, resulting in potentiation of the compound spinally evoked motor potentials. The interactive and synergistic effects indicate multi-segmental convergence of descending and ascending influences on the neuronal circuitries during electrical spinal cord stimulation. Our findings have important clinical implications for multi-site electrical spinal cord stimulation, especially when there is a need to potentiate spinal neuronal circuitries during functional tasks, such as locomotion and standing.

Acknowledgments

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Highlights

- Transcutaneous electrical spinal stimulation is a valuable tool for neurorehabilitation
- Effects and mechanisms of multisite spinal cord stimulation were investigated
- The interactive and synergistic effects were demonstrated using paired stimuli
- Multisite electrical spinal cord stimulation has important clinical implications

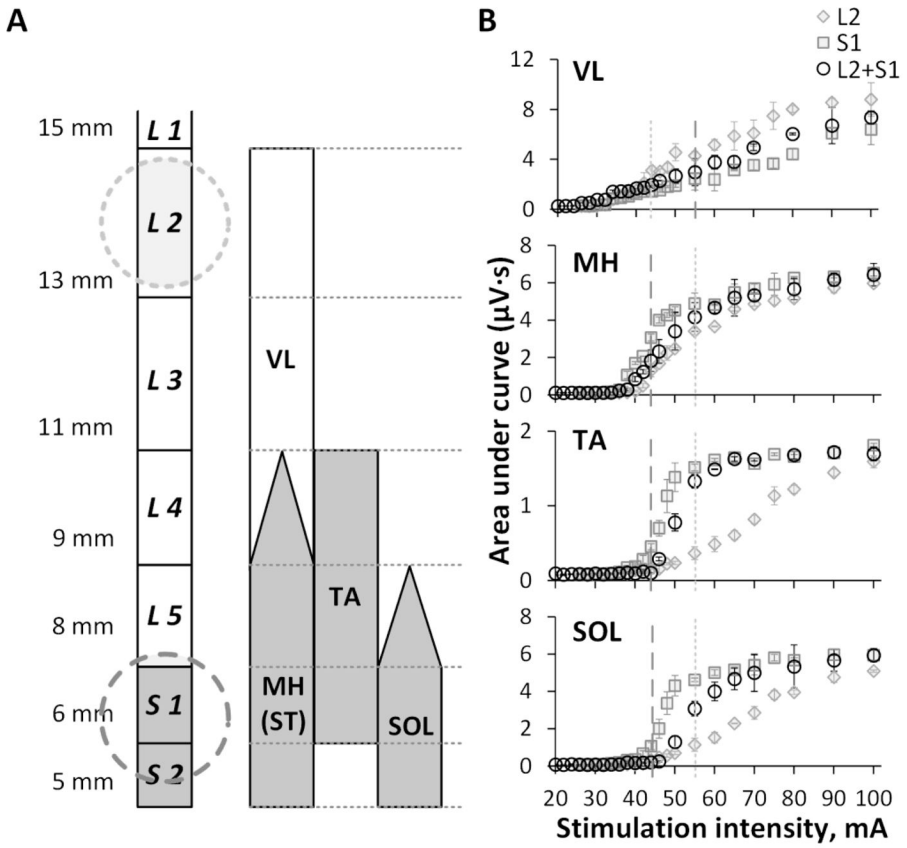

Figure 1.

(A) Reconstruction showing the approximate location of transcutaneous electrical spinal cord stimulation over the lumbosacral enlargement, and the location of the motor pools based on the segmental charts provided by Kendall et al. (1993). Triangle endings in the chart denote agreement of three to four sources out of six from the anatomical and clinical data; whereas square ending bars denote motor pools' localization agreed on five or six sources. The numbers shown left at each spinal segment are the average length in millimeters of the segment (Sharrard, 1964). Dotted and dashed circles correspond to approximate location of T10 and L1 vertebral levels of the stimulation, respectively. (B) Recruitment curves of the right leg muscles obtained at each (L2, S1) and both (L2 and S1, simultaneously) locations of spinal stimulation. Dotted and dashed lines indicate the stimulation intensities used during paired stimulation delivered at ~T10 and ~L1 vertebral levels (L2 and S1 spinal segments), respectively. VL, vastus lateralis; MH, medial hamstrings; TA, tibialis anterior; SOL, soleus muscles.

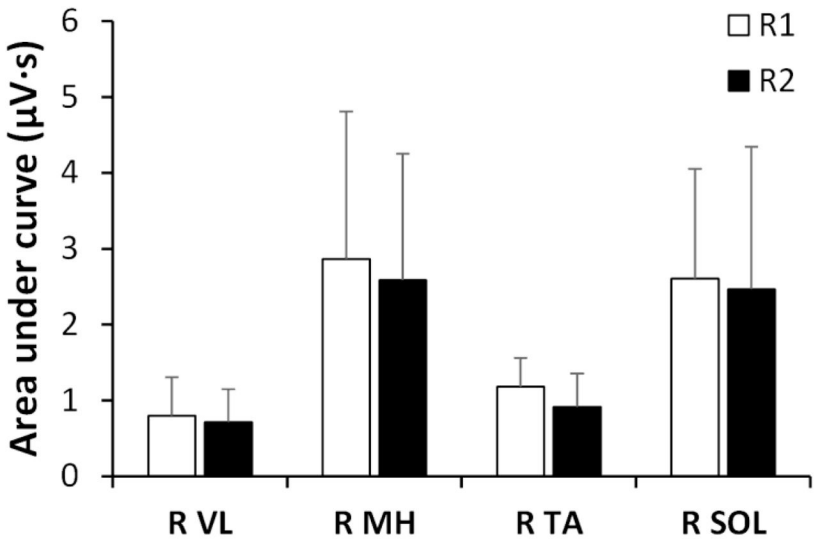

Figure 2.

The average magnitudes (area under the curve) of single responses of the right leg muscles during single transcutaneous electrical spinal cord stimulation delivered at ~T10 and ~L1 vertebral levels (L2 and S1 spinal segments). VL, vastus lateralis; MH, medial hamstrings; TA, tibialis anterior; SOL, soleus muscles.

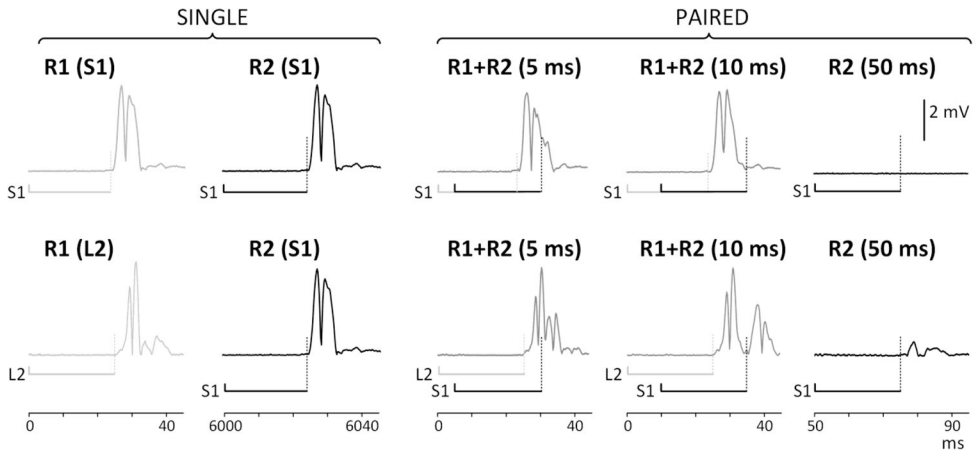

Figure 3.

Rectified and averaged spinally evoked motor potentials in one participant during paired transcutaneous electrical spinal cord stimulation delivered with CTIs of 5, 10, and 50 ms during S1-S1 (top) and L2-S1 (bottom) paradigms. Red and blue traces indicate the conditioning and test responses, respectively. At the diagrams presenting the CTIs of 5 and 10 ms, brown traces show the compound R1+R2 response. At the diagrams presenting the CTI-50, the conditioning, only test response is shown. Horizontal lines below the potentials' waveforms indicate the stimulation channel, and the dotted lines present the onset of the conditioning (red) and test (blue) responses. Scales on the bottom indicate the time in ms from the onset of the conditioning stimulus.

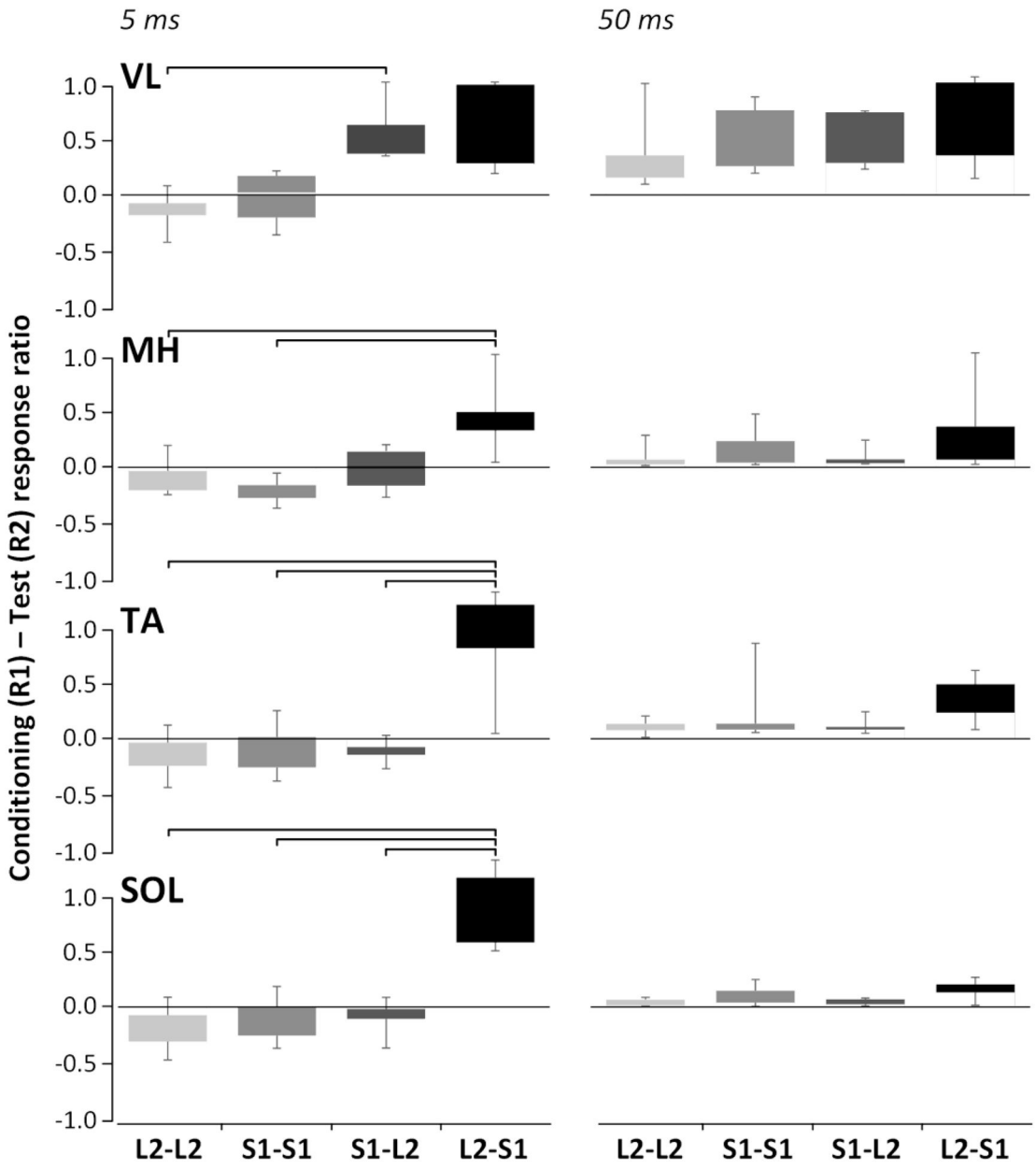

Figure 4.

Pooled data illustrating the amount of post-stimulation modulation occurred when the paired stimulation was delivered with at CTI-5 (left) and CTI-50 (right) at various vertebral levels. The results are summarized in boxplots with the box as the 25–75th percentile, and the whiskers as the highest and lowest values. Positive values indicate that the compound R1+R2 response was larger than the R1, whereas negative values indicate that the compound response was smaller than the R1. Horizontal bars indicate significant differences between different stimulation locations ($p < 0.05$).