Neuromodulation of evoked muscle potentials induced by epidural spinal cord stimulation in paralyzed individuals

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Abstract

Epidural stimulation of the lumbosacral spinal cord has been used to facilitate standing and voluntary movement after clinically motor complete spinal cord injury. It seems of importance to examine how the epidurally evoked potentials are modulated in the spinal circuitry, and projected to various motor pools. We hypothesized that chronically implanted electrode arrays over the lumbosacral spinal cord can be used to functionally assess spinal circuitry linked to specific motor pools. The purpose of this study was to investigate the functional and topographic organization of compound evoked potentials induced by the stimulation. Three individuals with complete motor paralysis of the lower limbs participated in the study. The evoked potentials to epidural spinal stimulation were investigated after surgery in supine position, and in one participant during both supine and standing with body weight load of 60%. The stimulation was delivered with intensity from 0.5 to 10V at a frequency of 2Hz. Recruitment curves of evoked potentials in knee and ankle muscles were collected at three localized and two wide-field stimulation configurations. Epidural electrical stimulation of rostral and caudal areas of lumbar spinal cord resulted in a selective topographical recruitment of proximal and distal leg muscles, as revealed by both magnitude and thresholds of the evoked potentials. Epidural stimulation activated both afferent and efferent pathways. The components of neural pathways that can mediate motor evoked potentials were highly dependent on the stimulation parameters and sensory conditions, suggesting a weight-bearing induced reorganization of the spinal circuitries.
**Introduction**

In humans, lumbosacral epidural electrical stimulation can facilitate standing and voluntary movement after complete motor paralysis (Harkema et al. 2011). It has also been shown that non-patterned epidural stimulation (ES) applied to lumbar spinal cord can induce stepping-like patterns of EMG activity in leg muscles in individuals with complete spinal cord injury (SCI) (Dimitrijevic et al. 1998; Gerasimenko et al. 2003; Harkema et al. 2011; Minassian et al. 2007b). We have begun to examine how the potentials evoked via an epidural electrode array, are modulated in the spinal circuitry, and projected to different motor pools. We also observed how the epidurally evoked potentials are modulated by sensory input projecting to a spinal cord that has not received any input from the brain for more than two years. These observations provide the groundwork for understanding how the spinal circuitry of an injured spinal cord can respond to a range of pharmacological agonist and inhibitors of excitatory and inhibitory receptors known to be important in facilitating standing and stepping after a complete spinal cord injury in adult rats (Musienko et al. 2011).

We hypothesize that chronically implanted electrode arrays over the lumbosacral spinal cord in individuals with complete motor paralysis of the lower limbs can be used to functionally assess spinal circuitry linked to specific motor pools. To test this hypothesis we have asked the following questions: Are the modulatory features of epidurally evoked potentials spatially unique when the stimulus is induced at different anatomical points along the lumbosacral spinal cord relative to the anatomical location of the sensory-motor pathways being modulated? To what degree can such spatially unique pathways be selectively activated by different stimulation configurations? How is the composition of evoked muscle potentials affected by location and extension of the spinal cord stimulation? Finally, are the potentials uniquely modulated when the subject is in a supine or standing position?
Methods

Participants

Three individuals with SCI participated in this study (Table 1). Participants provided written informed consent to the experimental procedures, which were approved by the University of Louisville (KY, USA) and the University of California, Los Angeles (CA, USA) institutional review boards.

Epidural electrical spinal stimulation

A stimulation unit (RestoreADVANCED, Medtronic, Minneapolis, MN, USA) in combination with a 16-electrode array (5-6-5, Medtronic, Minneapolis, MN, USA) implanted at the T11–L1 vertebral levels over the spinal cord segments L1–S1 as described previously (Harkema et al. 2011), were used to deliver electrical stimulation to the lumbosacral enlargement of the spinal cord (Fig. 1). The electrode array was positioned over the midline of the exposed dura. The neurosurgeon performed the initial placement based on anatomical landmarks and fluoroscopy. The array’s location was also adjusted using electrophysiology during the surgery. Bilateral evoked potentials from leg muscles were collected and evaluated in detail by spatial, temporal, and amplitude characteristics, to optimize the location and symmetry of the electrode array placement. Once the electrodes’ position was optimized and confirmed, the array was sutured in place.

The evoked potentials to epidural spinal stimulation were investigated 2 to 3 weeks after the surgery. The experiments were performed with the individual relaxed in a supine position. In participant A45, the data was also recorded during standing with body weight load (BWL) of 60%. The Bodyweight Support System (Innoventor, St Louis, MO, USA) with a harness in combination with manual assistance were used to provide body weight support during standing. The stimulation current had a rectangular, biphasic, pulse waveform with a pulse duration of 210 μs. Using 0.5 V increments, the stimulation intensity was increased from 0.5 to 10 V, or the maximum tolerable intensity, whichever was less. In some cases, the stimulation caused a tightness in the abdominal area at higher intensities; therefore, maximum intensity was kept
below the level which would cause difficulty breathing. At each intensity, minimum of 5 stimuli were delivered at a frequency of 2 Hz. Recruitment curves were collected at three localized bipolar (5-//6+, 8-//7+, 10-//9+) and two wide-field (0-/5-/11-/4+/10+/15+, 0+/5+/11+/4-/10-15-) stimulation configurations (Fig. 1).

EMG Recording and Data Collection

Surface electromyogram EMG signals were recorded bilaterally using bipolar surface electrodes (Motion Lab Systems, Baton Rouge, LA, USA) that were placed longitudinally on the soleus (SOL), medial gastrocnemius (MG), tibialis anterior (TA), vastus lateralis (VL), rectus femoris (RF), medial hamstrings (MH), and gluteus maximus (GL) muscles with fixed inter-electrode distance of 17 mm. EMG signals from the iliopsoas muscles (IL) were recorded with fine-wire electrodes (MA-416, Motion Lab Systems, Baton Rouge, LA, USA). In addition, two surface electrodes placed symmetrically lateral to the electrode array incision site over the paraspinal muscles were used to record the stimulation artifact. The artifact was later used to define the onset of the stimulus. Reference electrodes were placed bilaterally over the distal part of tibia bone. The EMG signals were differentially amplified using MA300 EMG System (Motion Lab Systems, Baton Rouge, LA, USA) with a band-pass filter of 10 Hz to 2 kHz (-3 dB). Finally, the EMG data were digitized at a sampling rate of 2000 Hz. The power density of the signal was tested to ensure that there was negligible signal power beyond 500 Hz.

Data analysis

The digitized MG, TA, VL, MH, GL, and IL EMG time series were full-wave rectified after subtraction of the mean background EMG. The latency of the response was defined as the time between the stimulus and the moment when the EMG activity reached levels higher than the mean baseline EMG plus three times its standard deviation. The magnitude of the evoked potentials was calculated by measuring the area under the curve across each component. Based on findings from previous studies (Andersen et al. 2003; Gerasimenko et al. 2006; Lavrov et al. 2006), three components of the evoked potentials, which are attributed to involvement of
different pathways were analyzed: early (ER) and medium (MR) responses, as well as the long latency response (LLR). The onset of ER was determined based on the latency of the earliest response of a given muscle on each stimulation configuration across all stimulation intensities. The duration of ER was determined from the ensemble averaged waveform displayed on a computer monitor; in case it was impossible to distinguish visually the ER and MR, the onset of MR was defined as 10 ms after the onset of ER on the basis of reported latencies and durations (Gerasimenko et al. 2006; Lavrov et al. 2006). For the MR duration, a constant interval of 30 ms was used. In addition, the LLR was processed in a 60- to 250-ms post-stimulation interval during wide-field stimulation configurations during supine and standing with BWL of 60% in participant A45 (Andersen et al. 2003).

The evoked potential magnitude for each muscle was reported as a ratio with respect to the maximum value across all stimulation configurations. The proportion of activation of different extensors or flexors attributable to each stimulation area was then calculated for each participant. The latencies of the evoked potentials for each muscle in different configurations for each individual were analyzed using repeated measures analyses of variance (ANOVA). Where appropriate, F-statistics were corrected for violations of the sphericity assumption using the Greenhouse-Geisser procedure. A simple t-test comparisons with Bonferroni correction were made to decompose significant effects involving more than two means ($\alpha = 0.05$). The two-way interactions for each participant and muscle are depicted on Fig. 6. Results of the pooled data are presented as mean values ± standard deviations (SD).

**Results**

The stimulation resulted in visible single twitches in multiple muscles at higher stimulation intensities. Hip flexors, knee flexors, and plantarflexors dominated the force, so a bilateral hip/knee flexion and plantarflexion were observed. On the EMG, however, the threshold for evoked potentials occurred consistently at a lower stimulation intensities compared to when twitches became visually apparent. The properties of the evoked potentials reflected the relative
rostro-caudal position of the respective motor pools. Figure 2 demonstrates the averaged evoked potentials (n = 5) obtained during localized rostral (A) and caudal (B) stimulation at different intensities in participant B13. The magnitude of the potentials in most muscles was dependent on the location of the stimulation site. The potentials in proximal muscles, such as IL or VL, occurred with larger magnitude at the rostral configuration (Fig. 2A), whereas the responses in distal muscles, such as MG or TA, occurred at lower stimulation intensities and had the largest magnitude using the caudal configuration (Fig. 2B).

Figure 3 provides some perspective on the level of specificity in selecting different combinations of motor pools using our electrode array. This can be accomplished by stimulating with the anode and cathode closely spaced, as well as with the anode and cathode at the maximum distance. There was a relationship between the magnitude of evoked potentials during localized and wide-field stimulation configurations for each participant. Further, there were several common characteristics in the stimulus-response relationships in different stimulation configurations across all three participants. First, the magnitude of the responses was dependent on the following variables: i/ stimulation delivered via rostral electrodes of the array primarily activated proximally located IL, ii/ stimulation delivered via medium portion of the array activated primarily knee muscles: VL and MH, iii/ stimulation delivered via caudal electrodes of the array activated predominantly distally located MG and TA, as well as GL. Second, thresholds of the muscle activation were dependent on the stimulation configuration: during wide-field stimulation, the thresholds were lower, and occurred at the intensities as low as 1 V. Third, the pattern of the recruitment curves in many cases was different during wide-field stimulation as compared to the localized one, i.e. initial increment of the response’s magnitude was followed by its decay with subsequent secondary increment of the magnitude. The latter occurred at higher stimulation intensities, and the response’s magnitude during that was often two to three times larger than during the first increment. During localized stimulation, the magnitude of the response increased in a more linear fashion, and either reached a plateau or had a tendency to decrease at higher stimulation intensities. Finally, when the stimulation location was “non-specific” for a given muscle, a substantial increment in the response magnitudes remained so at maximum stimulation intensities (for instance, see IL during localized caudal stimulation in
participant B13, and MG and TA during localized rostral stimulation in all participants). In addition to the common characteristics, there also were distinguishing differences in the evoked potentials between participants (Fig. 3). For instance, in participant B13, the amplitude of GL was prominent in localized rostral stimulation configuration, whereas in participants A45 and B07, higher activation of GL occurred in localized caudal configurations. Another example was that VL potentials across localized versus wide-field stimulation configurations in different participants. In subject B13, the greatest magnitude of VL potentials occurred in localized middle configuration, whereas in participant B07, the largest VL potentials were evoked in wide-field stimulation configurations.

On the other hand, a striking example of similarities among subjects was evident in the cumulative level of activation in different muscles during localized rostral and caudal stimulation configurations with increasing intensities of stimulation in three participants (Fig 4). Predominant activation of IL during rostral stimulation, and GL, MG, and TA during caudal stimulation can be clearly seen across all individuals.

Fig. 5 shows the shape and latency of evoked potentials in MG compared to the TA in participant B07 during localized (A) and wide-field (B) caudal stimulations. During wide-field stimulation, the latency of the responses changed as a function of stimulation intensity. In the MG, the onset of the response shifted without a noticeable change in the ER magnitude, whereas in the TA, the shift was accompanied by an increase of the ER (Fig. 5B, 5 – 10 V). Fig. 5C depicts recruitment curves of ER and MR during the localized and wide-field stimulations. During wide-field stimulation, there was an initial increment of MR preceding the ER, with a subsequent decrement in its magnitude at 4.0 V, followed by the second magnitude increment. The stimulus-response relationships of ER and MR were different in MG and TA, with a predominant occurrence of MR in MG, and ER in TA. The latencies of the evoked potentials for each muscle in different configurations for each individual did not differ during localized stimulation, whereas during wide-field stimulation, the latency was significantly shorter in most muscles at the maximum stimulation intensity (Fig. 6).

In the supine position, the changes of the ER and MR components of the evoked responses during wide-field stimulation differed substantially from those recorded during standing (BWL
of 60% in participant A45) (Fig. 7-8). The thresholds of the responses were considerably lower in supine as compared to the standing position (Fig. 7A-B, 8). The magnitude of the ER and MR was larger in MG during standing (Fig. 7A), and in TA during supine (Fig. 7B). The MR amplitudes were higher during standing (Fig. 7B, 8B). A dramatic difference between the two positions occurred in the LLR (Fig. 7C, 8). In the supine position, the LLR was prominent only in flexors (TA, IL, MH), whereas that was suppressed in extensors (except of VL during rostral stimulation) (Fig. 7C, 8). The most pronounced occurrence of the LLR was present during the mild to medium stimulation intensities, and its manifestation seemed to be reciprocal with the ER and MR development (Fig. 8, TA and IL). During standing, the LLR was suppressed in flexors: completely in TA and MH, and substantially in the IL; whereas, the irregular and asynchronous long latency activity was present in the extensors (MG) (Fig. 7C).

Discussion
We demonstrated that epidural electrical stimulation of rostral and caudal areas of lumbar spinal cord results in a selective topographical recruitment of proximal and distal leg muscles, as revealed by both magnitude and thresholds of the evoked potentials. We also found that the threshold, structure, and latency of the responses changed with the stimulation intensity at different electrode configurations, suggesting an activation of different components, length and complexity of the transmitting pathways. Further, our findings demonstrate an example of the difference in the structure of the responses evoked during standing as compared to those in supine position, suggesting a weight-bearing induced reorganization of the spinal circuitries.

Spatiotemporal patterns of motor pool activation along the rostro-caudal axis of the spinal cord
Many myotomal maps have been published on the approximate rostro-caudal location of motor neuron pools innervating different muscles in the human spinal cord, derived from various sources, including autopsy, clinical, neuroimaging, and electrophysiologic studies (see
(Wilbourn and Aminoff 1998) for a review). Nevertheless, some variation in the topographical root innervation of muscles remains debatable, and all myotomal charts can usually be considered only as “approximate guides”, given that anomalous innervation occurs frequently (Ivanenko et al. 2006; Phillips and Park 1991; Stewart 1992). Also, motor neuron density might exhibit inter-segment, inter-muscle, and inter-subject variability (Arber 2012; Ivanenko et al. 2006). Moreover, most muscles are innervated by and project sensory information extensively to excitatory and inhibitory neurons associated with multiple motor pools among several spinal segments.

In our study, we compared the proportion of activation of extensors and flexors attributable to each stimulation area, instead of evaluation the absolute values of each muscle recruitment curve in different segments. We assumed that the optimal site and configuration of stimulation of particular muscles can be derived from their relationships at each configuration. Our data are generally consistent with the anatomy and myotomal maps of the spinal cord and lumbosacral roots (Altman and Bayer 2001; Ivanenko et al. 2006; Kendall et al. 1993; SHARRARD 1955; SHARRARD 1964): epidural stimulation of rostral and caudal areas of lumbar spinal cord resulted in a predominant activation of proximal and distal muscles’ motor neuron pools, respectively (except of GL). Figures 3 and 4 demonstrate remarkable consistency in the pattern of different muscle recruitment during localized rostral and caudal stimulations across all three participants. Importantly, however, the order of the proximal to distal muscles’ recruitment cannot be described as a simple linear relationship between the rostral and caudal stimulation sites. Such “non-location specific” responses occurred during higher stimulation intensities delivered through wide-field configurations, and were characterized by high magnitude of the evoked responses in both proximal and distal muscles. This phenomenon to some degree might be expected given that most muscles are innervated by several spinal segments, and the network of motor neurons appears to be widely spaced over extensive regions of the spinal cord (Arber 2012; Ivanenko et al. 2006). Another contributing factor is that, current flows through the well-conducting cerebrospinal fluid surrounding the spinal cord and in the vertebral canal (Holsheimer 1998; Ladenbauer et al. 2010; Minassian et al. 2007a). Thus, spinal roots from multiple adjacent segments can be stimulated with even relatively narrowly placed electrodes at
localized stimulation configuration. But in spite of this broad area of excitation, it appears that spatiotemporal patterns of spinal cord activations can have surprisingly specific consequences on motor behavior and therefore has important clinical implications (Gad et al. 2013).

While previous studies provide a basis from which it is possible to predict the properties of evoked potentials when stimulating with different parameters and at different sites along the spinal cord, none of these data were derived from individuals with chronic, complete motor paralysis (greater than 2 years post injury), and none were obtained for obvious ethical reasons via chronically implanted epidural electrodes in uninjured subjects. Here we show the feasibility of the method and provide the beginning of a comprehensive data base that can be used to compare primordial spinal circuitry properties across individuals with different injuries, as well as for repeated measures over time within the same individual. The spatiotemporal maps of the neural networks that lead to different motor pools along the rostro-caudal axis of the human spinal cord may be used to selectively control and monitor the output state and plasticity of the neural network in the course of recovery of motor functions in patients with various motor disorders. The person data are consistent with the conclusion that the selective recruitment of the specific motor neuron pools can be titrated during localized stimulation of the spinal cord, particularly at lower stimulation intensities (Gad et al. 2013).

**Epidural stimulation can activate both afferent and efferent pathways**

Previous studies in animals have described different components of the evoked potentials: early (ER) and middle (MR) responses, which were attributed, at least in part, to the preferential involvement of efferent (motor neurons, anterior roots), and afferent (posterior roots, group Ia and II) structures, correspondingly (Gerasimenko et al. 2006; Lavrov et al. 2006). We have applied similar approach to our data. An analysis of ER and MR recruitment curves during wide-field stimulation configurations has revealed that in many cases, their relationship was reciprocal: the increment of ER was often accompanied by a substantial decrement of MR (Fig. 5C, Fig. 8). With increasing intensity, the stimulus-response relationship in many muscles shares some characteristics with the H-reflex and M-wave recruitment curve, that is, was characterized by two peaks of the response magnitude increment separated by a period of depression, with
early, low threshold, small, short-lasting peak, and late, higher threshold, large, reaching a
plateau increment. These findings suggest that the lower stimulation intensities result in initial
recruitment of the lower threshold afferent structures; whereas, with a progression of the
intensity, more of efferent volleys are involved causing an occlusion effect of the afferent
pathways, and leading to an activation of motor neurons and/or anterior roots. This notion is
supported by significant decrement of the responses’ latency at maximum intensities of the
stimulation (Fig. 5, Fig. 6), and concur with prior reports obtained in experiments with
transcutaneous spinal cord stimulation (Minassian et al. 2007a). We suggest that localized
stimulation produces complete recruitment of targeted afferent structures, allowing more focused
motor neurons’ activation; whereas, wide-field stimulation activates afferent and inter-segmental
efferent structures which contribute to both MR and ER, and can be clearly distinguished from
each other at maximum stimulation intensities.

Previous electrophysiological (Hunter and Ashby 1994; Maertens de et al. 1988; Minassian et al.
2004; Murg et al. 2000) and computational (Ladenbauer et al. 2010; Rattay et al. 2000) studies
have reported that the structures directly, electrically stimulated by lumbar spinal cord
stimulation are predominantly afferent fibers of the posterior roots. It has been demonstrated that
the segmental effects of spinal cord stimulation resulted from the simultaneous orthodromic and
antidromic activation of the central projections of primary afferents (Hunter and Ashby 1994). It
has been also suggested, that the volleys elicit segmental muscle responses in the lower limbs,
and co-activate lumbar interneuronal circuits via synaptic projections (Jilge et al. 2004;
Minassian et al. 2004; Minassian et al. 2007a). The degree, to which different components of the
spinal networks are activated, however, is to a large extent a function of the site and stimulation
parameters. Also, it is important to recognize that the present experiments are designed to
characterize the responsiveness of the spinal networks associated with a given motor pool at
relatively high voltages. This contrasts with a stimulation strategy in which we prioritize an
“enabling” stimulation scenario, which includes intensities of stimulation near or below motor
thresholds. This stimulation strategy allows the spinal circuits to process both peripheral sensory
and supraspinal inputs, for instance, to facilitate the control of movement (Harkema et al., 2011).
In this case, the excitability of interneuronal circuits can be more extensively modulated in absence of or rarely occurring direct activation of motor pools (Gad et al. 2013). Also it is important to recall that most if not all descending pathways are non-functional in individuals with complete motor paralysis, and therefore the impact of stimulation via the dorsal columns in mediating evoked responses would conceivably differ from that of the uninjured spinal cord. Although of scientific interest, it is not realistic to investigate the structures being activated via implanted epidural electrode array in individuals with intact spinal cord. The difference between the threshold, composition, latency, and stimulus-response relationship of the evoked potentials during localized and wide-field stimulation configurations are consistent with the interpretation that spinal cord electrical stimulation activates the intraspinal structures (Danner et al. 2011; Partanen et al. 2000). The difference in the responses evoked in the supine and standing positions in present study also supports this point. We acknowledge a probability of the both direct and indirect involvement of the intraspinal structures during spinal stimulation. The amount of contribution of each mechanism during epidural stimulation can be different though, than during other methods, for instance, during transcutaneous stimulation. This difference, in turn, may be critical for the therapeutic and functional efficacy of those approaches.

**Neuromodulatory effects during standing**

It is plausible that changes in the geometry of the thoraco-lumbar spine and the relative position of the electrode array can influence the flow of current (Ranger et al. 2008), and thus, can contribute to the observed difference in the neuromodulation of the evoked potentials during supine and standing positions. Further studies during movements and in different positions are required to investigate this in details. At the same time, it is well known that functional load through weight-bearing activities plays a significant role in modulating spinal motor neuron excitability during human posture and movement (Harkema et al. 1997; Knikou et al. 2009; Kozlovskaya et al. 2007; Nakazawa et al. 2004). Proprioceptive, cutaneous tactile, and nociceptive afferent inputs are known to converge onto spinal interneurons in the reflex pathway (Schomburg 1990; Zehr and Stein 1999). As such, spatial and temporal summation of activity in
different afferent projections can be attributed to the effects observed during standing. However, few studies have investigated the capacity to gate afferent input via spinal circuitry among different motor neuron pools in people with SCI (Dietz 2010; Dy et al. 2010; Knikou et al. 2007). Positive augmentative interaction between the epidural spinal stimulation and sensory activity during stepping on a treadmill has been demonstrated previously in cats with SCI (Gerasimenko et al. 2008; Gerasimenko et al. 2003; Guevremont et al. 2006), as well as in individuals with incomplete SCI (AIS C) (Herman et al. 2002). In the present study, we demonstrated in individuals with motor complete paralysis (AIS A and B) that the relationship between the different components of evoked responses is different at the same stimulation configurations during supine and standing positions.

The difference in the magnitude of the earlier latency components (ER and MR) with their larger magnitude in extensors during standing, and in flexors during supine position, suggest higher excitability of extensors and inhibition of flexors during weight-bearing. It may seem contradictory to the previous findings on the inhibitory effects of the peripheral sensory inputs on the extensors’ motor pool, specifically – on the soleus H-reflex, in non-disabled individuals (Brooke et al. 1997; Koceja et al. 1995; Stein 1995). This could be explained, however, by the difference in the amount of inhibitory control of spinal circuits between the individuals without and with SCI, as well as by the larger contribution of the spinal interneuronal network during epidural spinal stimulation. As it has been previously shown the spinal lesion deprives the relevant pathways of a tonic excitatory drive and/or removes tonic inhibitory control of a spinal circuit (Pierrot-Deseilligny and Burke 2005; Taylor et al. 1984). On the other hand, as oppose to the soleus H-reflex which is a response from a single muscle, the potentials evoked by the spinal epidural stimulation engage the lumbar cord networks, including the interneuronal circuits. As such, the excitatory status of the extensors and flexors during spinal stimulation reflects the intraspinal, inter-segmental, and multisensory interaction differently, than during the H-reflex test. This notion can be supported by the findings on the LLR modulatory effects during supine and standing.

It has been suggested previously that the LLR reflect activation of polysynaptic circuitry associated with the flexor reflex afferent (FRA) system, and may underlie the voluntary, standing
and stepping motor activity (Dimitrijevic et al. 1998; Gerasimenko et al. 2006; Musienko et al. 2011). For instance, during locomotion, the withdrawal pattern is highly dependent on the present motor task, indicating that proprioceptive input and spinal motor systems functionally modulate the withdrawal pattern (Andersen et al. 2003; Crenna and Frigo 1984; Duysens et al. 1990; Zehr and Stein 1999). In the present study, the balance between the magnitude of the LLR in extensors and flexors was shifted toward flexors during the supine position, and towards extensors during standing. A prominent flexors’ activation in rest is most likely associated with propriospinal connectivity between the hip flexor and ankle flexor motor neuron pools (Grillner 1985). Smaller flexors activation relative to extensors during standing has been observed previously in non-disabled participant (Andersen et al. 2003; Rossi and Decchi 1994), and is associated with maintaining the equilibrium (Paquet et al. 1996). It has been shown that the plantarflexors are more excitable for Ia afferent inputs than dorsiflexors, while the reverse is true for corticospinal inputs (Pierrot-Deseilligny and Burke 2005). Compared with the supine position, the more prominent LLR in extensors most likely reflects changes in motor neuron excitability based on the multi-sensorial convergence on spinal reflex pathways (Schomburg 1990). Therefore, the characteristics of the evoked potentials cannot be attributed only to a certain excitation level of the motor pools inside the spinal circuits, but eventually rely on the interplay of multiple peripheral sensory resources and related interneurons.

It has been recently suggested that individuals with SCI gradually lose some intrinsic properties of spinal circuitry as they progress from the acute to the chronic state, supporting that the loss of sensory and motor input leads to re-organization of the underlying spinal networks (Ashby et al. 1974; Calancie et al. 1993; Hiersemensel et al. 2000; Skinner et al. 1996). However, our findings showing that the state of excitability of lumbar cord networks can be effectively modulated during such functional task, as standing, look promising in light of the functional rehabilitation of individuals that can occur at the chronic stages after the injury (Harkema et al. 2012).

Our data provide evidence that in the absence of supra-spinal descending drive, the human lumbosacral spinal circuitries can gate afferent input during weight bearing. As shown in animals after complete spinal transection, as well as in human subjects with complete motor paralysis, this state-dependent modulation of potentials demonstrates the important role of the spinal
interneuronal networks in processing complex sensory input in the regulation of the motor output generated during standing and locomotion.

Conclusion

Stimulation of rostral and caudal areas of lumbar spinal cord via epidurally-placed electrodes results in a relatively selective activation of proximal and distal motor neuron pools. Epidural stimulation can activate both afferent and efferent pathways. The neural pathways that can mediate motor evoked potentials to all muscles of the lower limbs are highly dependent on the stimulation parameters. Depending on these parameters and sensory environment, the pathways mediating these responses can have both monosynaptic and polysynaptic, and orthodromic and antidromic components. Stimulation limited to a more localized set of electrodes within an electrode array allows more selective activation of proximal and distal and flexor and extensor motor pools. Wide-field stimulation results in a more generalized pattern of activation among proximal and distal muscles. Our findings provide a better understanding of the mechanisms by which the general levels of excitability of specific neuronal networks within the spinal circuitry are modulated with varying stimulation parameters. As these neural mechanisms become more apparent, epidural stimulation techniques applied to the injured spinal cord will become increasingly more valuable as an electrophysiological and clinical assessment tool.

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Reference List


Figure captions

Figure 1. Schematic presentation of the 16-electrode array (left panel), and corresponding spinal cord segments L1–S1 (right panel). Drawing is an estimation and might not be representative for each participant.

Figure 2. Evoked potentials in participant B13 during localized rostral (5-/6+) (A) and caudal (10-/9+) (B) stimulation configurations in supine position. The average of 5 non-rectified responses is shown for each stimulation intensity from 0.5 V to 10 V with increment of 0.5 V. GL, gluteus maximus; IL, iliopsoas; VL, vastus lateralis; MH, medial hamstrings; MG, medial gastrocnemius; TA, tibialis anterior muscles. Arrows indicate the onset of the stimulus. Bold black lines indicate the threshold of MG and TA response. Cathode (active) and anode (reference) electrodes are shown in black and red, respectively.

Figure 3. Area of the evoked potentials (sum of early and medium responses) in extensors and flexors recorded in supine position during localized (5-/6+, 8-/7+, 10-/9+) and wide-field (0-/5-/11-/4+/10+/15+, 0+/5+/11+/4-/10-15-) stimulation configurations normalized to the maximum response of each muscle in all configurations. GL, gluteus maximus; IL, iliopsoas; VL, vastus lateralis; MH, medial hamstrings; MG, medial gastrocnemius; TA, tibialis anterior muscles. Cathode (active) and anode (reference) electrodes are shown in black and red, respectively.

Figure 4. Cumulative area of the evoked potentials (sum of early and medium responses) in extensors and flexors recorded in supine position during localized rostral (5-/6+) (A) and caudal (10-/9+) (B) stimulation configurations normalized to the maximum response of each muscle. GL, gluteus maximus; IL, iliopsoas; VL, vastus lateralis; MH, medial hamstrings; MG, medial gastrocnemius; TA, tibialis anterior muscles. Cathode (active) and anode (reference) electrodes are shown in black and red, respectively.

Figure 5. Evoked potentials in participant B07 during localized (10-/9+) (A) and wide-field (0+/5+/11+/4-/10-15-) (B) caudal stimulation configurations. The average of 5 non-rectified responses is shown for each stimulation intensity. Orange dashed lines show the epochs of early (ER) and medium (MR) responses determined based on the latency of the earliest response of a
given muscle at all stimulation intensities. Red dotted lines indicate the changes of the onset of
the response with increment of the stimulation intensity. (C) Area of the early (ER) and medium
(MR) responses during localized (left panels) and wide-field (right panels) stimulation
configurations in the supine position. MG, medial gastrocnemius; TA, tibialis anterior muscles.
Cathode (active) and anode (reference) electrodes are shown in black and red, respectively.

Figure 6. The average latencies of the evoked potentials during localized (5-//6+, 8-//7+, 10-//9+)
and wide-field (0-//5-/11-//4+/10+/15+, 0+/5+/11+/4-//10-15-) stimulation configurations at
threshold and maximum intensities. The average of 5 responses is presented for each stimulation
intensity. GL, gluteus maximus; IL, iliopsoas; VL, vastus lateralis; MH, medial hamstrings; MG,
medial gastrocnemius; TA, tibialis anterior muscles. Cathode (active) and anode (reference)
electrodes are shown in black and red, respectively. Asterisks indicate statistically significant
differences between the values at the threshold and maximum stimulation intensity (* p < 0.05).

Figure 7. Evoked potentials (early (ER) and medium (MR) responses) in participant A45 during
wide-field caudal (0+/5+/11+/4-//10-15-) stimulation configuration in medial gastrocnemius
(MG) (A) and tibialis anterior (TA) (B) in the supine and standing (BWL = 60%) positions. The
average of 5 non-rectified responses is shown for each stimulation intensity. Orange dashed lines
show the epochs of the early (ER) and medium (MR) responses. (C) The long latency responses
(LLR) in medial gastrocnemius (MG), tibialis anterior (TA), and iliopsoas (IL) are presented for
both positions at the stimulation intensity of 3.5 V. The thin lines indicate individual trials,
whereas the bold lines indicate the average of 5 trials recorded in the supine (blue) and standing
(red) positions. Orange dashed lines show the epoch the long latency (LLR) responses. Cathode
(active) and anode (reference) electrodes are shown in black and red, respectively.

Figure 8. Area of the early (ER), medium (MR), and long latency (LLR) responses in participant
A45 during wide-field rostral (0-/5-/11-/4+/10+/15+) (upper panels) and caudal (0+/5+/11+/4-/
/10-15-) (lower panels) stimulation configurations in the supine (A) and standing (BWL = 60%)
(B) positions. Left axis correspond to the LLR values. Note that the recruitment curve during
standing was not recorded at the higher stimulation intensities due to discomfort experienced by
the participant. MG, medial gastrocnemius; TA, tibialis anterior; VL, vastus lateralis; MH,
medial hamstrings; IL, iliopsoas muscles. Cathode (active) and anode (reference) electrodes are
shown in black and red, respectively.
Table 1

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<th>Years since injury</th>
<th>LOI</th>
<th>AIS</th>
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The motor score is based on the examination of 10 key muscles on each side. For each movement, force is measured and assigned a coefficient from 0 (absence of muscle contraction) to 5 when contraction creates a movement in all the joint amplitude against a complete resistance. Light touch and pinprick sensitivity was assessed on a 0-2 scale at each of 28 dermatome (0-absent, 1-impaired, 2-intact) on each side. The presented scores are given as total out of 50 for each (left and right) side.

LOI = Neurological Level of Injury = Most Caudal Segment with normal motor and sensory function as per the International Standards for the Classification of Spinal Cord Injury. AIS = American Spinal Injury Association Impairment Scale.
Figure A shows the cumulative area (normalized to maximum response) of extensors and flexors for GL, IL, VL, MH, MG, and TA muscles across different stimulation intensities (V). Figure B displays similar data for another set of muscles.

Cumulative area (normalized to maximum response) is plotted against stimulation intensity (V) for each muscle group. Each line represents a different muscle or condition, indicated by the legend on the right.