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Intraspinal microstimulation for the recovery of function following spinal cord injury

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Abstract

Spinal cord injury is a devastating neurological trauma, often resulting in the impairment of bladder, bowel, and sexual function as well as the loss of voluntary control of muscles innervated by spinal cord segments below the lesion site. Research is ongoing into several classes of therapies to restore lost function. These include the encouragement of neural sparing and regeneration of the affected tissue, and the intervention with pharmacological and rehabilitative means to improve function. This review will focus on the application of electrical current in the spinal cord in order to reactivate extant circuitry which coordinates and controls smooth and skeletal muscle below the injury. We first present a brief historical review of intraspinal microstimulation (ISMS) focusing on its use for restoring bladder function after spinal cord injury as well as its utilization as a research tool for mapping spinal cord circuits that coordinate movements. We then present a review of our own results related to the use of ISMS for restoring standing and walking movements after spinal cord injury. We discuss the mechanisms of action of ISMS and how they relate to observed functional outcomes in animal models. These include the activation of fibers-in-passage which lead to the transsynaptic spread of activation through the spinal cord and the ability of ISMS to produce fatigue-resistant, weight-bearing movements. We present our thoughts on the clinical potential for ISMS with regard to implantation techniques, stability, and damage induced by mechanical and electrical factors. We conclude by suggesting improvements in materials and techniques that are needed in preparation for a clinical proof-of-principle and review our current attempts to achieve these.

Keywords

Electrical stimulation; lumbosacral enlargement; locomotor networks; standing; walking; muscle fatigue

Introduction

Functional electrical stimulation (FES) refers to the application of electrical current to peripheral or central neural tissues to restore function after injury. Most commonly, FES is applied to peripheral nerve fibers; however, central stimulation may be advantageous as it affords the opportunity to activate directly the higher level circuitry which oversees and coordinates function. Intraspinal microstimulation (ISMS) is an example of a central stimulation paradigm which employs fine microwires implanted into the lumbar spinal cord. This area of the spinal cord contains all of the motoneurons which innervate muscles of the lower limbs (Henneman and Mendell, 1981) along with the networks which coordinate

muscles and produce multijoint synergies and locomotion (Jankowska, 1992; Kiehn, 2006). The lumbar cord also offers structural advantages as it is protected by the spinal column and is distant from actuated muscles, thus reducing the chance of damage or dislocation of the implanted microwires. The current work is a review of our results with ISMS and a commentary on the works of other groups employing ISMS to answer their own research questions.

A brief history of ISMS in research

ISMS has been used extensively as a research tool to explore spinal network pathways. As early as 1940, Renshaw used penetrating electrodes to stimulate in the spinal cord and measure the synaptic delay in reflex pathways (Renshaw, 1940). In the 1970s, Jankowska and colleagues undertook a series of mapping experiments designed to explore the connections between interneurons mediating reciprocal inhibition (Jankowska and Roberts, 1972) and to understand the way in which external current activates neuronal structures in the CNS (Gustafsson and Jankowska, 1976).

The mapping of spinal cord networks

More recently, ISMS has been used by Bizzi and colleagues to investigate the organization of locomotor circuitry in the spinal cord of frog (Bizzi et al., 1991; Giszter et al., 1993; Lemay et al., 2001; Saltiel et al., 2001), rat (Tresch and Bizzi, 1999), and cat (Lemay and Grill, 2004; Lemay et al., 2009). These authors employed penetrating microelectrodes to stimulate in the intermediate gray matter (primarily lamina VII) and evoke movements around the hip, knee, and ankle joints. Forces were measured in a matrix of locations in order to calculate the isometric force vectors which resulted from ISMS of the intermediate gray matter. As a result of this work, these authors hypothesized that the intermediate gray matter is autonomously organized into circuits which, when activated individually, produce a finite number of convergent force fields that will direct the limb to an equilibrium point in space (Fig. 1). They termed these “movement primitives” and suggested that all movements were constructed from these simpler components (Bizzi et al., 1995). Further, descending connections could employ these circuits to construct more complex movements by activating movement primitives in combination.

Although the movement primitives hypothesis is attractive, experiments that we have performed led us to believe that the intermediate spinal gray matter does not contain discrete circuits that govern specified movements. Our results showed that the outcome of intermediate spinal cord stimulation depended strongly on the presence of descending input (Mushahwar et al., 2004). Further, the direction of movement could be altered by increasing stimulus amplitude. This suggests a complex and flexible network in the spinal cord, perhaps responsible for processing inputs in order to activate motoneuronal pools coordinately.

The restoration of bladder control

In the early 1970s, experiments were performed investigating the ability of penetrating spinal cord electrodes to produce voiding in spinal cord injured individuals. Trials were initially conducted in animals and early results proved promising (Fig. 2). Approximately 50% of the animals achieved functional voiding during acute experiments with spinally intact ($n = 11$) and transected cats ($n = 9$; Friedman et al., 1972). Chronic experiments in cats and dogs produced similar results and suggested that, given accurate placement, penetrating spinal cord electrodes might be an effective method of reestablishing normal voiding after spinal cord injury (SCI) in humans. Based on this work, 27 human patients with paraplegia were implanted with bilateral penetrating electrodes at the S1 spinal cord level (Nashold et al., 1981). Adequate voiding was achieved in ~60% of these patients, the

majority of the successful outcomes occurring in females (10 out of 15 successes were in women). Coactivation of the external urethral sphincter (EUS) necessitated further interventions such as partial sphincterotomies in some patients (Nashold et al., 1981). This, combined with the ~40% failure rate attributed to misplacement of the electrode tips, led the authors to conclude that other treatments could produce similar efficacy without the need for invasive spinal cord surgery (Gaunt and Prochazka, 2006).

More recent experiments have employed ISMS using smaller microwire electrodes. It was thought that the smaller surface area of the electrode tips (1600–2400 μm^2) might avoid the current spread likely responsible for the coactivation of bladder and EUS (Pikov et al., 2007). A number of sacral sites exist that might be targeted by ISMS in order to produce coordinated bladder contractions and EUS relaxation. In one report, sites along the sacral spinal cord were stimulated in α -chloralose anesthetized, spinally intact cats while bladder and urethral pressures were recorded (Grill et al., 1999). The authors found moderate increases in bladder pressure; however, these were sometimes associated with increases in urethral pressure, indicating coactivation of the EUS. Nevertheless, distinct sites were located which produced solely increases in bladder pressure along with no increase or even small decreases in urethral pressure. Another group applied ISMS in the S2 region through a single microwire in both acute and chronically transected cats (Tai et al., 2004). Despite demonstrating large increases in bladder pressure, with small decreases in urethral pressure, voiding was limited due to coactivation of EUS. In a more recent report employing chronically implanted ISMS arrays, some degree of voiding was achieved with at least one microwire in 15 of 22 cats (Pikov et al., 2007). The authors of this study encountered results ranging from near-complete voiding to no voiding with any microwire. In some cases, ISMS produced sustained and large increases in bladder pressure and concomitant decreases in EUS tone, while in other animals, a sufficient combination of bladder pressure and EUS relaxation could not be achieved. The authors speculated that these mixed results were explained by having too few stimulation sites available in each animal. It is likely that a denser array of intraspinal stimulating sites would have produced a higher success rate. The authors concluded that interwire spacing of no greater than 300 μm should be employed (Pikov et al., 2007).

To date, ISMS has not proved effective in producing bladder voiding consistently better than established devices which employ anterior sacral root stimulation and often posterior rhizotomy (Ragnarsson, 2008). Therefore, some have concluded that employing it to restore lower urinary tract function after SCI in humans may not be worth the risks associated with long-term implantation (Gaunt and Prochazka, 2006). However, the possibility that ISMS can inhibit EUS contraction has persuaded other groups to continue to pursue multisite arrays which could provide the ability to selectively contract and relax the bladder and EUS, respectively, in order to produce continence or micturition (Pikov et al., 2007).

Use of intraspinal microstimulation for restoring leg movements

A description of surgical techniques

Over the past decade, our group has been actively investigating the use of ISMS for producing functional standing and walking movements after SCI. Testing was conducted in rats and cats, with or without an SCI, and the investigations involved short- and long-term ISMS implantation protocols. Below, we summarize the findings and experiences we have amassed.

Detailed explanations of our surgical methods in rat and cat have been published elsewhere (Bamford et al., 2010b; Guevremont and Mushahwar, 2008). What follows is a brief overview of the general implantation procedure. Microwires are manufactured manually

from 30 μm diameter fine wire composed of stainless steel or 80%/20% platinum/iridium and insulated with a 4- μm layer of polyimide (California Fine Wire Company, Grover Beach, USA). Microwires are exposed by manually deinsulating 30–60 μm of the terminal end and sharpening the tips by cutting them to $\sim 15^\circ$. Under anesthesia, a laminectomy is performed to expose the target region of the spinal cord. Intraspinal microwires are implanted in both sides of the spinal cord, spaced 2–4 mm apart, rostrocaudally. Arrays comprising multiple microwires are implanted with the tips targeting the motoneuronal pools along the lumbar spinal cord. Microwire tips are inserted individually and advanced to preset depths so that the epidural portion floats on the dorsal surface of the spinal cord. During implantation, test trains are delivered through each microwires to verify accurate targeting of its tip. For instance, trains of stimuli through a microwire tip resting in the quadriceps motoneuronal pool of cat or rat would produce selective activation of quadriceps muscle and evoke gradual increases in force in response to increasing stimulus amplitude. Individual microwires are fixed at their point of insertion to the dura mater with discrete drops of cyanoacrylate glue. The microwires are further secured in bundles to the dura mater with 8–0 sutures at the base of the nearest rostral spinous process. At this spinous process, the microwires are routed through a silastic tube that is already anchored to the laminar surface of the process. The tube is subcutaneously routed to a headpiece anchored to the skull and the micro-wire connector is exteriorized through the skin to allow for electrical connections (Fig. 3).

Following chronic implantation, animals are administered analgesics and antibiotics and allowed to recover for 7 days. After the initial recovery period, test stimulus trains (typically 100–200 μA , charge-balanced, biphasic pulses with a width of 200 μs and frequency of 20–50 pulses/s) are delivered to ascertain the microwire responses. Direct observation and palpation ensure that the microwires continue to evoke specific and robust contractions of the target muscles and that force is recruited in a gradual manner. Changes in the direction of movement or the rate of the force recruitment likely indicate a shifting of the microwire tip during the recovery period. Typically, the movement patterns and force recruitment evoked by chronically implanted wires will not change after this initial recovery period (Mushahwar et al., 2000). However, stimulus thresholds may continue to rise in the 2- to 4-week period after implantation, a result we attribute to the gradual accumulation of connective tissue encapsulation around the microwire.

ISMS is best applied in the motoneuronal pools for evoking functional limb movements

In our experiments, ISMS is typically applied in lamina IX of the lumbosacral spinal cord. The motoneurons contained therein are organized into discrete columnar groups according to the muscles they innervate (Henneman and Mendell, 1981; Romanes, 1964). Motoneuronal pools are conserved across species, their locations having been confirmed in rats, cats, and humans (Nicolopoulos-Stournaras and Iles, 1983; Romanes, 1951; Sharrard, 1955; Vanderhorst and Holstege, 1997). We have shown previously that delivering current directly in the motoneuronal pools activates muscles selectively (Mushahwar and Horsch, 2000b; Mushahwar et al., 2000), and recruits force gradually in response to increasing stimulus strength (Bamford et al., 2005; Mushahwar and Horsch, 2000a; Snow et al., 2006). Further, a range of movements can be elicited; from single-joint flexion or extension, to weight-bearing and fatigue-resistant standing and stepping (Lau et al., 2007; Saigal et al., 2004; Fig. 4). All of these are routinely achieved in the absence of the pharmacological aids that are typically required to generate weight-bearing and functional movements via epidural or dorsal horn stimulation (Barthelemy et al., 2006, 2007; Gerasimenko et al., 2003; Ichiyama et al., 2008). Finally, in spinally intact cats, ISMS at amplitudes up to 300 μA produced no signs of pain or discomfort, suggesting that this method could be used in

individuals with partial spinal cord injuries for functional rehabilitation (Mushahwar et al., 2000).

The movements recruited by ISMS

From single joints to functional stepping

Early work established that ISMS can selectively activate muscles and produce gradual force recruitment (Mushahwar and Horch, 2000a,b). Further, stimulation through single microwires can produce whole-limb synergies characterized by the production of weight-bearing torque at the joints of spinally intact cats (Mushahwar et al., 2000).

Interleaved stimulus trains through pairs of microwires in each side of the spinal cord produced a mean standing duration of 21 min when a closed-loop control strategy was employed in spinally intact cats (Lau et al., 2007). In animals with chronically transected spinal cords, functional stepping was achieved by delivering interleaved stimulus trains through microwire arrays implanted in the lumbosacral cord (Saigal et al., 2004). Individual microwires producing extension, flexion, and limb-swing synergies were then activated coordinately to achieve stepping which was weight bearing and fatigue resistant over continuous bouts of 40 consecutive steps each. Stepping was achieved with only four microwires in each side of the spinal cord. As confirmed later this is evidence that ISMS can activate locomotor networks and produce rhythmic, weight-bearing stepping when applied in the ventral horn of the lumbosacral enlargement (Guevremont et al., 2006).

Presumably, single-joint movements are achieved by activating discrete motoneuronal pools, whereas synergies are achieved by activating multiple pools through existing spinal connections. Alternating stepping movements are likely achieved by the activation of an even larger network involving ipsilateral and bilateral reciprocal inhibitory connections (Guevremont et al., 2006; Jankowska, 1992; Prochazka et al., 2002).

The advantages of interleaved stimulation

One of the advantages of ISMS is the ability to employ interleaved stimulation strategies. Interleaved electrical stimulation can be used to improve fatigue resistance and produce smooth, predictable movements (Mushahwar and Horch, 1997; Rack and Westbury, 1969). Interleaving involves the presentation of stimulus pulses from multiple electrodes at evenly spaced intervals such that the resultant frequency of muscle activation is the sum of the individual pulse trains. For example, two electrodes stimulating at 20 pulses/s, when interleaved, would produce an aggregate 40 twitches/s in the muscle. In order to employ interleaved stimulation, an FES system must be able to recruit independent populations of motor units selectively. Others have employed interleaved stimulation to increase the fatigue resistance of evoked movements (McDonnall et al., 2004; Yoshida and Horch, 1993). Likewise, we have found that the fatigue resistance of ISMS can be improved by employing interleaved stimulation (Lau et al., 2007; Mushahwar and Horch, 1997; Fig. 5). The improvements offered by interleaving the stimulus trains are dependent upon the ability of ISMS to activate different subsets of motor units.

Explaining the recruitment characteristics of ISMS

Another advantage of ISMS is the observation that the delivery of current from a point source within discrete motoneuronal pools is capable of generating complex synergistic movements. This suggests that ISMS is capable of exciting a large network of neurons that connect motoneuronal pools into functional groups. In addition to the columnar motoneuronal pools, the ventral gray matter is known to contain a dense network of axonal processes from a variety of interneurons, propriospinal neurons, and afferent projections. It

has previously been established that networks do exist between synergistic motoneuronal pools and that they process the reciprocal activation of agonist and antagonist muscles (Jankowska, 1992). As one example, the branching of Ia afferents is known to be extensive as each axon synapses with every motoneuron in the homonymous motoneuronal pool and with a large proportion of motoneurons in pools of synergistic muscles (Mendell and Henneman, 1971). This suggests that motoneurons, in response to ISMS, are recruited transsynaptically via the excitation of fibers-in-passage, an attractive theory as it explains the following observations.

1. Gradual force recruitment. The force recruited by ISMS increases gradually in response to increasing stimulus strength (Bamford et al., 2005; Mushahwar and Horch, 2000a; Snow et al., 2006). We found that the slope of the average force recruitment curve in rats was 3.4 times and 4.9 times shallower than that derived from peripheral nerve stimulation (Bamford et al., 2010a, 2005). Further, as stimulus strength is increased, the duration of muscle twitches narrows and the proportion of fast-twitch fibers recruited by ISMS increases (Bamford et al., 2005; Mushahwar and Horch, 2000a). These responses approximate the small-to-large (and slow-to-fast) recruitment of motor units during reflex activation of a muscle, sometimes referred to as Henneman's size principle (Gordon et al., 2004; Henneman et al., 1974). As in Henneman's original experiments, our results could be explained by the indirect activation of motor units through afferent Ia projections (among other projections), which produce a normal, ordered recruitment (Henneman, 1957).
2. Whole-limb synergies can be generated by stimulating through a single microwire. Both flexion and extension synergies are readily achieved across a variety of neural contexts including spinally intact, spinally transected, and decerebrate cat preparations (Mushahwar et al., 2000; Saigal et al., 2004; Stein et al., 2002). The activation of distant motoneuronal pools required to achieve a synergy implies that a network of propriospinal neurons, interneurons, and afferents is transmitting the original activation via transsynaptic mechanisms (Mushahwar et al., 2002). Moreover, these synergies are relatively robust to perturbations such as the addition of anesthesia or varying stimulus characteristics such as pulse amplitude or frequency. This is in contrast to what is achieved during stimulation of the intermediate gray matter where responses are altered following spinalization, decerebration, or even as a result of increasing stimulus amplitude (Aoyagi et al., 2004; Mushahwar et al., 2004).

The production of single-joint movements can be explained by the activation of a single motoneuronal pool. Nonetheless, the activation of complex synergies must involve a larger network. It is understood that the first network elements activated by electrical stimulation are likely to be axons passing near the current source (fibers-in-passage; Gustafsson and Jankowska, 1976; Nowak and Bullier, 1998). The best explanation for the phenomena listed above is that ISMS activates motoneurons indirectly, that is, transsynaptically, through the excitation of fibers-in-passage, a result that has been demonstrated previously during stimulation of the spinal cord (Gaunt et al., 2006; Jankowska and Roberts, 1972).

The stability of ISMS implants

ISMS causes minimal histological damage

In chronic experiments, we have found that ISMS implants produce stable results and cause limited damage. We have performed postmortem histological examinations of spinal cord tissue obtained from chronically implanted cats and rats. We found evidence of ongoing inflammation limited to the area surrounding the microwire tracks in rats implanted for 30

days (Bamford et al., 2010b). In these experiments, rats were stimulated daily at levels sufficient to cause functional quadriceps contractions, but within safe limits for central neural stimulation (McCreery et al., 1990, 2004). In contrast to our rat experiments, we found no sign of ongoing inflammatory actions in cats implanted for up to 6 months and stimulated 2–3 times per week (Prochazka et al., 2001). This likely indicates that the inflammatory response endemic to centrally implanted, nonabsorbable structures such as microwires can be expected to subside over time so long as the applied electrical stimulus is within safe levels (Grill et al., 2009) and the implants are stable within the spinal cord tissue.

The flexibility of ISMS implants

Other investigations involving centrally implanted electrodes have shown lasting damage as evidenced by a decrease in the neuronal density surrounding the implant (Biran et al., 2005, 2007). One difference between these implants and our own is their mechanical properties. Electrodes made of silicon, tungsten, or another brittle material may create a mechanical mismatch between the electrodes and the soft tissue into which they are implanted. In contrast to these experiments, the minimal level of damage incurred by chronic ISMS implants is comparable to that seen in postmortem analysis of deep brain stimulation implants in human subjects (Haberler et al., 2000). This work demonstrated the formation of a glial scar surrounding the electrodes, but no ongoing inflammatory response despite the persistent use of the implants over a period of up to 70 months. Both ISMS microwires and deep brain stimulation electrodes are characterized by a degree of flexibility which may ameliorate the mechanically adverse effects of implantation by absorbing micromotion in the system. In support of this view, an experiment showed that free-floating silicon implants produced less cortical neural damage than when the same implants were tethered to the skull (Biran et al., 2007). Presumably, the floating implant design was able to move freely with the cortical tissue, while the tethered design resisted any micromotion. With regard to ISMS, it is our view that a design where each microwire floats independently and is composed of the most flexible materials which make implantation practical should be employed in order to produce the least amount of damage.

The functional stability of ISMS

A further indication of microwire stability can be derived from the stability of functional measures over time. Presumably, stability in key characteristics of ISMS such as stimulus threshold, force recruitment, and the observable movements produced suggest that the underlying neural structures recruited by ISMS have been maintained throughout the implantation period. Conversely, changes in these characteristics may indicate either movement of the microwire tip or damage to activated neural structures, or both. For instance, we determined that ISMS continues to recruit force gradually after chronic implantation and stimulation (Bamford et al., 2010b). Further, the functional movements elicited by ISMS microwires have been shown to be relatively stable as at least 67% of implanted microwires maintained the same responses over 6 month experiments in cats (Guevremont and Mushahwar, 2008; Mushahwar et al., 2000). In chronically implanted cats and rats, we have found that stimulus thresholds for activation have either risen (cats; Mushahwar et al., 2000) or fallen (rats; Bamford et al., 2010b) over the 30 days following implantation. While seemingly contradictory, these findings may be explained by the different stimulation durations employed in these experiments. In the cat experiments, the animals received little stimulation for the first 30 days following implantation and the increase in threshold for activation is presumably due to the encapsulation of microwires during this period. Following the initial rise, stimulus threshold was stable over the following months. In contrast, chronically implanted rats received 4 h of stimulation each day at levels sufficient to cause functional quadriceps activation. We speculate that daily stimulation may have induced a plastic response similar to that seen with daily step training

in chronically transected cats and rats which resulted in a decrease in markers of inhibitory neurotransmitters in the spinal cord (Edgerton et al., 2004). Although stimulus threshold changes were altered in a statistically significant manner in both chronically implanted cats and rats, the alterations did not cause the stimulus amplitude required to produce functional responses to rise beyond safe levels for central stimulation (McCreery et al., 1990, 2004).

Moving toward clinical application

Improvements necessary for clinical translation

The results we summarize here encourage the continuation of research into ISMS with the goal of progressing toward clinical proof-of-principle in the future. However, a number of challenges must be addressed before clinical trials could be considered. These challenges require further engineering as they are primarily related to microwire manufacture, implantation, and post-implantation control strategies.

Our results suggest that centrally implanted electrodes should be manufactured from the most flexible, compliant materials possible and implanted in a manner that allows the microwires to individually float with spinal cord micromotion. Currently, we accomplish this by implanting each microwire individually and manually. This occasionally leads to misplacement of the microwire tips, an occurrence that is often due to difficulties in perceiving the relative vertical axis with respect to the spinal cord (Guevremont and Mushahwar, 2008). It would be desirable to simplify the procedure by implanting an array of microwires in one step, so long as the mechanical individuality of each microwire is maintained. Current work is proceeding into the development of implantation systems which could temporarily connect multiple microwires but then dissolve in the tissue, leaving the microwires separated. A bioabsorbable material such as a hydrogel or collagenous platform might serve to contain the microwires during implantation, dissolving thereafter.

The manufacture of ISMS arrays is currently a manual, challenging process requiring 2–3 days per array. Once constructed, the arrays are fragile and cannot be further customized during implantation. One advance that we are currently employing is the use of magnetic resonance imaging prior to implantation in order to acquire accurate dimensions with which to customize each implant to the experimental animal. This allows us to manufacture fewer arrays and improves targeting success.

Conclusions

ISMS produces graded, fatigue-resistant force from selected muscles. Further, the movements generated include weight-bearing standing and stepping, despite the employment of relatively simple stimulation protocols and control strategies to date. We have found that chronic implantation of ISMS microwires is well tolerated by rat and cat spinal cord tissue and we believe that this is partly due to the flexible nature of our microwires. Advances in the materials and design of our implants will seek to capitalize on the inherent advantages of ISMS and aid in the development of a clinically viable procedure to restore motor function following SCI. If clinically successful, this technique could dramatically improve the quality of life and independence of those living with paralysis.

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Fig. 1.

Forces produced by stimulation of spinal cord gray matter in frog are measured at multiple locations in a grid. Force vectors are interpolated and a convergent force field is produced representing the equilibrium point for the generated movement. A limited number of distinct force fields (movement primitives) are identified. In theory, movement primitives could be combined in a modular manner to produce the full range of possible movements. Reproduced with permission from Bizzi et al. (1995).

Fig. 2.
ISMS for bladder control. A drawing of the early spinal stimulation methods used in animals and humans to restore bladder function after spinal cord injury. Reproduced with permission from Nashold et al. (1972).

Fig. 3.

A drawing of the ISMS implant array. Multiple microwires can be inserted at varying lengths along the spinal cord, creating a bilateral array of possible stimulation sites. The microwires are covered in plastic film and routed through a silicon tube to a headpiece. Reproduced with permission from Prochazka et al. (2001).

Fig. 4. Summary of ISMS microwire tip locations and evoked responses. The locations of stimulation across multiple cat experiments are displayed in (a). A variety of movements could be produced from microstimulation but the most reliable came from microstimulation of lamina IX. Flexion movements were most common at all spinal segments tested; however, extension and alternation could also be reliably produced (b). Reproduced with permission from Guevremont et al. (2006).

Fig. 5.

Fatigue characteristics of interleaved stimulation. Normalized tetanic forces produced by stimulating cat spinal cord through two independent electrodes (A and B) are shown. Single forces were produced by stimulating through either electrode A or B individually at 50 Hz (single A and single B). Refractory AB forces were produced by stimulating electrode B at 50 Hz during the refractory period for neurons activated by electrode A. Interleaved stimulation was produced by stimulating through each electrode in an interleaved manner at 25 Hz, yielding an aggregate stimulation frequency of 50 Hz. Not only did interleaved stimulation produced greater force, but it also reduced fatigue. Reproduced with permission from Mushahwar and Horch (1997).