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# RESTORING WALKING AFTER SPINAL CORD INJURY

Bradley J. Holinski[1,2], Alex Paquet[1], Patrice Topart[1], Dirk G. Everaert[3], Richard B. Stein[4], Vivian K. Mushahwar[3]
*[1]INO, Quebec, Canada*
*[2]Department of Biomedical Engineering, University of Alberta, Alberta, Canada*
*[3]Division of Physical Medicine and Rehabilitation, University of Alberta*
*[4]Department of Physiology, University of Alberta*

## ABSTRACT

A spinal cord injury may cause paralysis and altered motor, respiratory, and bladder function. Intraspinal microstimulation can be used to activate latent motor networks in the ventral horn of the spinal cord that remain intact below the lesion level after a traumatic spinal cord injury. Previous work in cats has shown that ISMS activates networks of neurons in the lumbosacral region of the spinal cord and produces co-ordinated multi-joint movements, which tend to be fatigue-resistant. In this work, we demonstrate that ISMS produces over ground walking in adult cats for distances nearing 1 km. One of the main challenges in producing functional walking is the spatial targeting of motor networks within the spinal cord. An electrode is under development that contains multiple independent stimulation sites along the length of the electrode to improve the probability of stimulating the target region. These developments might eventually help to restore functional walking after spinal cord injury.

## INTRODUCTION

There are 1.3 million people in the USA living with a spinal cord injury (SCI)[1]. These injuries adversely affect motor and sensory function, often disrupting grasping, walking, breathing and bladder function, and reducing the quality of life of the affected person and their family [2]. Regaining the ability to walk is a high priority for people with paraplegia [2]. Unfortunately, interventions to restore walking after a SCI have had limited success to date [3]. One of the most promising techniques involves the use of electrical stimulation for activating muscles and nerves. This technique, commonly known as functional electrical stimulation (FES), produces large forces adequate for supporting the body while standing. However, the rapid rate of muscle fatigue has limited the distances of walking to less than 100 m, which hinders the clinical acceptance of these walking systems [3, 4].

Intraspinal microstimulation (ISMS) is an FES technique that stimulates the spinal cord through implanted microwires and has been shown to produce strong fatigue-resistant movements [5, 6]. Activation sites for all of the movements required for walking exist within the lumbosacral cord, and their relative locations within the spinal cord have been mapped [7, 8]. To target these activation sites, multiple electrodes are implanted in a single anatomical region, unlike peripheral stimulation that requires leads at multiple locations in the hindlimbs. Stimulation through a single microwire can produce single-joint or coordinated multi-joint movements (i.e. synergy) [5]. Additionally, these networks recruit motor units in a near-normal physiological order by activating fatigue-resistant muscle fibers at lower current amplitudes [9].

To date, ISMS has produced fatigue-resistant standing [5] and over ground walking in an animal model [10]. We hypothesized that ISMS, in conjunction with appropriate stimulation control strategies, can produce sustainable fatigue-resistant over-ground walking.

## METHODS

All experimental procedures were approved by the University of Alberta's Animal Care and Use Committee. Five intact male cats (4.2-5.5kg) were used in acute, non-recovery experiments. Each cat was anaesthetized (pentobarbitol) and a laminectomy was performed from L4 to L6 to expose the dorsal spinal cord. A fine-wire array consisting of 12 electrodes per side was implanted bilaterally (Pt-Ir 80-20%, 50µm diameter, 0.1mm deinsulated tip). Hip and knee flexors, knee extensors, and a full limb extensor synergy were targeted for each side based on existing maps of motor neuron pools [7, 8]. After implantation, the cats were transferred to an instrumented walkway (walkable length of 2.9m) and partially suspended in a cart-mounted sling and maintained under anesthesia. Motion tracking markers were fixed to the right hindlimb to record kinematics with a camcorder (120fps, JVC Americas Corp., Wayne, NJ, USA). Markers were placed on the iliac crest, hip, knee, ankle and metatarsophalangeal joints. Accelerometers and gyroscopes were fixed to both hindlimbs and were sampled at 1kHz using Cerebus (Blackrock Microsystems, Salt Lake City, UT, USA). Force transducers mounted under the walkway plates captured independent left and right supportive forces (vertical).

A 16 channel current controlled stimulator delivered trains of pluses (up to 120 µA, monophasic, 290 µs pulse width, 62 Hz) to the 8 electrodes per side producing best functional movements (determined qualitatively). During initial setup trials, appropriate stimulation amplitudes were established for the step states (E1, E2, E3 and F). For some trials, the controller processed incoming signals from external sensors (force transducers, accelerometers and gyroscopes) in real time with a moving average filter of 120ms in Matlab (MathWorks Inc., Natick, MA, USA). However, the analysis of the control strategy has been previously reported and not included in this work [11]. Experiments were terminated when the cat could no longer traverse the walkway or after 300 trials (whichever occurred first).

Immediately following the experiment, the cats were kept deeply anaesthetized and perfused intracardially with Formalin (4 % formaldehyde). The spinal cord was extracted with the implanted array in place and imaged using magnetic resonance imaging to determine the location of the electrode tips relative to the gray matter.

## RESULTS

ISMS produced walking across multiple trials up to a cumulative distance of 835m with the potential to walk even farther. In figure 1, we demonstrate that an ISMS-based system could produce similar walking in multiple subjects (i.e. all five cats). In the first 2 cats (A and B), the electrodes produced weaker movements requiring higher stimulation levels to elicit the desired response (figure 1A). They walked 189m and 84m, respectively. The remaining 3 cats (C, D, and E) each walked 300 trials across the walkway (maximum tested) of which at least 210 trials were considered successful during post-hoc analyses. These three cats successfully walked between 609m and 835m. Additional walking metrics are shown in figure 1B-D. Walking distances, kinematics and force production were similar across these cats.

Walking metrics were compared at the beginning and end of each experiment to determine the effect of fatigue. An average of the first 10 successful trials was compared to an average of the last 10 successful trials for cats C, D, and E. Peak ground clearance and stride length decreased from 11 to 7mm and 140 to 126mm, respectively. In addition, the supportive forces increased from 3.5 to 4.0N suggesting that by increasing stimulation amplitudes to compensate for changing kinematics, forces were inadvertently increased as well.

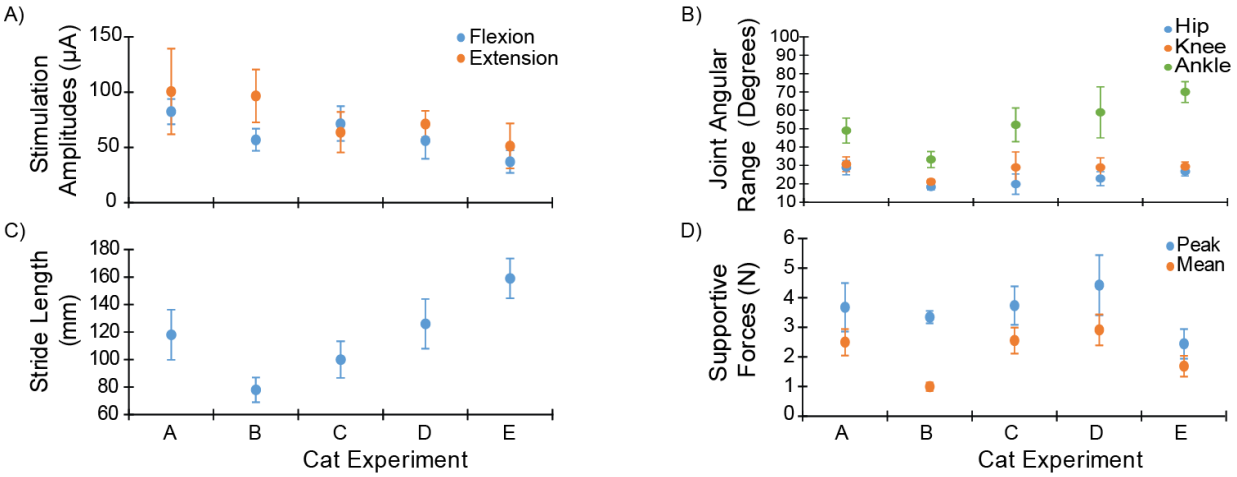


Figure 1: Comparison of the different parameters and walking metrics between experiments (cats A-E). (*(A) Stimulation amplitudes for flexors and extensors. (B) Joint angular range for hips, knees, and ankles. (C) Stride length. (D) Average peak and supportive forces.*)

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For each experiment, the tip locations of the selected electrodes were measured using magnetic resonance imaging. Across all experiments, 48 out of the 79 selected electrode tips were positioned in the gray matter (61%). The percentages of the tip locations in the gray matter were 94%, 56%, 50%, 50%, and 56% for cats A-E, respectively.

## DISCUSSION

We used ISMS to obtain over-ground walking of 835 m (roughly a 16 fold improvement over a previous study using intramuscular stimulation) with the potential to walk even farther. Kinematics and kinetics remained relatively constant and showed only minor decay over the course of the experiments.

ISMS elicited coordinated, multi-joint movements by activating intact spinal neural networks. Although a model with a transected spinal cord and no anesthesia would be an ideal demonstration for clinical feasibility, the goal of this work, to produce long distance walking until exhaustion, would not be feasible in an awake model. It is hypothesized that forces may be greater with removal of anaesthesia from the preparation, allowing lower initial stimulation amplitudes to produce equivalent forces. The anaesthesia may be reducing force output by dampening the networks in the central nervous system [12]. In previous work, ISMS has produced strong movements (up to 20N during stance) in absence of anesthesia [10, 12]. Although these results suggest that this proof-of-principle would be applicable to a chronic model of SCI, it will still be necessary to implement ISMS in a chronic spinalized cat model to confirm this hypothesis.

## FUTURE DIRECTIONS

One of the major challenges for a successful implant is stimulating the target motorpools within the spinal cord. The current ISMS array uses fine wires each with a single stimulation site.

We are currently developing multi-site electrodes (adapted from Snow *et. al*) that are printed on a fused silica or polymer substrate [13]. Multiple stimulation sites will improve the probability that a stimulation site will be implanted within close proximity to a target region. Only the stimulation sites that produce desirable movements will be used (since each stimulation site is an independent channel). The electrodes will be manufactured using microfabrication techniques that will eventually be able to produce large quantities, relatively cheaply. For implantation in the spinal cord, the dimensions of the cylindrical electrode are 80μm in diameter and 5mm in length (including a beveled tip). Electrically, they will have up to

six Pt-Ir stimulation sites printed along the shaft and will be insulated with parylene.

The design phase is ongoing. As a feasibility test, we have successfully printed gold traces on a cylindrical substrate (figure 2). In 2015, the electrodes are scheduled to be implanted in humans for acute, exploratory experiments.

These data show promise for ISMS to become an integral component of a neuroprosthetic device to restoring walking function in people with paraplegia.

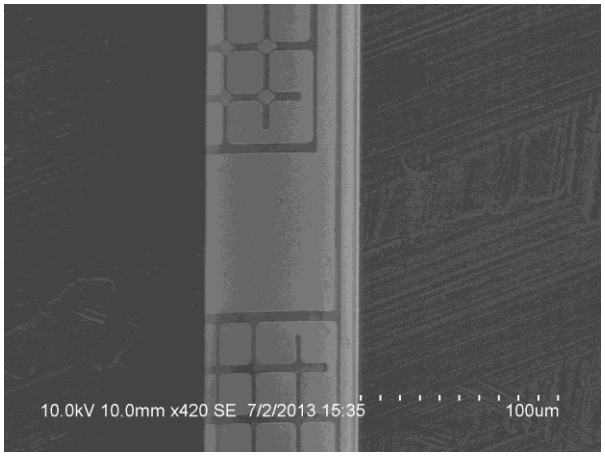


Figure 2: Test printing a pattern on an 80 µm diameter cylindrical substrate (image acquired with a scanning electron microscope).

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