Rodent Model for Forelimb Neuromuscular Stimulation Based Movement Therapy

Tsukasa Kanchiku1,3, James V Lynskey1, Toshihiko Taguchi3, James J. Abbas1, 2 and Ranu Jung1, 2

1 Center for Adaptive Neural Systems, The Biodesign Institute and 2 The Harrington Department of Bioengineering, Arizona State University, PO Box 85287, Tempe, AZ, USA.
3 Department of Orthopedic Surgery, Yamaguchi University School of Medicine, 1-1-1 Minami Kogushi, Ube, Yamaguchi 755-8505, JAPAN ranu.jung@asu.edu

Abstract
We present the development of a novel rodent model for neuromuscular stimulation assisted forelimb movement. The motor points for flexors and extensors of the shoulder, elbow, and digits were identified and the muscles were implanted with custom intramuscular stimulation electrodes. Strength-duration curves were generated to guide the choice of stimulation parameters required to produce consistent isolated contraction of each muscle with adequate joint movement. Using these stimulation parameters and previous locomotor EMG data, stimulation was performed on each joint muscle pair to produce reciprocal flexion/extension movements in the shoulder, elbow, and digits, while 3D joint kinematics were assessed (PEAK Motus). Additionally, co-stimulation of multiple muscles across multiple forelimb joints was performed to produce stable multi-joint movements similar to those observed during target reach-grasp-release movements. Future work will utilize this animal model to investigate mechanisms that promote functional recovery and neuromotor plasticity after cervical spinal contusion injury.

1. INTRODUCTION
‘Functional Neuromuscular Stimulation’ (FNS) is a rehabilitation strategy that applies low-level electrical current to the nerves that control muscles, to stimulate functional movements. It has been utilized to produce movement and a successful application has been developed for restoration of hand-grasp function in individuals with neurological disorders such as spinal cord injury and stroke (3, 5, 7-9, 11). Little, however, is known about the ability of upper extremity electrical stimulation to promote recovery of distal upper extremity function or plasticity within the central nervous system (1, 6, 10). Currently, there are no animal models of FNS-assisted upper extremity (forelimb) movement with spinal cord injury that could enable more controlled studies to assess the efficacy and the mechanisms involved in FNS-assisted target reaching-grasp-release. Initial development of such a model requires designing electrodes and mapping the appropriate stimulation electrode implantation sites to muscle motor points. It is also essential that the implanted electrodes provide sufficient recruitment of motor units to achieve appropriate contraction of the muscles. Here, we describe the development of a model to produce FNS-assisted forelimb movement (target reaching-grasp-release) in rodents. This rodent model of FNS-assisted forelimb movement will allow for assessment of mechanisms of neuromotor plasticity for this therapeutic rehabilitation technique.

2. METHODS

2.1. Animals and electrode implantation
Intact adult female Long-Evans rats (n=6, 250-300g) were anesthetized with Sodium Pentobarbital (40 mg/kg, ip) and given Isoflurane gas (0.5- 1.5%, inhaled) as a supplement to maintain anesthesia. Toe pinch and visual monitoring of respiration were used as indicators of adequate anesthesia level. Two animals were used to identify the location of the anatomical motor point of forelimb muscles. Two animals were used to determine the optimum stimulus condition that provides sufficient recruitment of motor units to achieve appropriate contraction of the each forelimb muscle. Two animals were used to produce rhythmic target reaching-grasp-release movement. Custom monopolar intramuscular stimulating electrodes were implanted in muscles acting at the shoulder (extensor/external rotator, spinodeltoideus, n=4; flexor/abductor, supraspinatus, n=4), elbow (extensor, triceps brachii, n=4; flexor, biceps – 274 –
brachii, n=4) and digit (extensor, extensor digitorum communis, n=4; flexor, flexor digitorum profundus, n=4) joints. The custom stimulation electrodes and implant procedure were similar to those used in a previous study conducted in our laboratory (4). The electrode leads were routed sub-cutaneously to the back where they were connected via an in-line connectors to a custom head connector (Omnetics Inc.).

2.2. Strength duration (SD) curves and stimulation kinematics

After the FNS electrode implantation surgery, anesthetized animals were placed upright with under belly support on a platform with all four limbs hanging unloaded. The head connector was connected to a stimulator (A-M Systems). In order to assess the whether the electrodes had been implanted close to the motor point, twitch threshold current strength duration (SD) curves were obtained. The twitch threshold current is defined as the minimum current required producing a visual twitch in the muscle. Stimulation was provided using multiple pulses at 75 Hz for 210 msec with biphasic (cathodic first) pulses with a width of 10, 20, 40, 70, 100, 300, or 500 $\mu$s per phase. The frequency for stimulation in this study was fixed at 75 Hz, since fused contractions were observed at this stimulus frequency in a previous study(4).

The joint angle data for the stimulated unloaded limb were collected using a kinematic system (Peak system, Peak Performance Technologies, Inc. Centennial, CO) as described in detail previously(12). Cone shaped three dimensional reflective markers (3M infrared reflective tape) were placed on the scapula (lateral aspect), shoulder (greater tubercle), elbow (lateral epicondyle), wrist, 3rd metacarpophalangeal joint, and distal digit (3rd digit) of the forelimb respectively. Two infrared cameras of the PEAK MOTUS system were focused to capture images of each of the reflective markers during limb movement on electrical stimulation. The stimulator driven in free run mode provided electrically isolated constant current pulses with either changing pulse width or current amplitude for neuromuscular stimulation of the forelimb muscles using the implanted FNS electrodes. The pulse widths used for stimulation were 40, 70, 100, and 300 $\mu$s/phase and two different current amplitudes (1.5 or 3 times the twitch threshold current at 40 $\mu$s) were used. The captured video data was then analyzed offline to determine the joint angles. The joint angles obtained were normalized with respect to the maximum angle range obtained at all current amplitudes and pulse widths tested. The proper stimulation parameters required to produce consistent isolated contraction of each muscle with adequate joint movement were determined using these joint angle data.

Using these parameters and previous locomotor EMG data(12), stimulation was performed on each joint muscle pair to produce reciprocal flexion/extension movements in the shoulder, elbow, and digits, while 3D joint kinematics were assessed. Additionally, co-stimulation of multiple muscles across multiple forelimb joints was performed to produce stable multi-joint movements similar to those observed during target reach-grasp-release movements using a custom computer controlled stimulator (FNS16 - CWE, Inc.).

3. RESULTS

The anatomical motor points for the spinodeltoideus, supraspinatus, triceps brachii, biceps brachii, extensor digitorum communis, and flexor digitorum profundus in the left forelimb were identified.  Figure 1 illustrates an example of this detailed anatomy of the muscles and their innervation (Only the supraspinatus is shown).

The supraspinatus (SS) was targeted for implantation to achieve shoulder flexion/abduction. This muscle is situated beneath the cervical trapezius (CT). It arises from the anterior margin of the scapula, from its vertebral border as far as the spine, from the superior surface of the spine, and from the whole supraspinous fossa. It is inserted by a tendon into the anterior margin of the head of the humerus.(2) The suprascapular nerve
innervates SS and the motor point is located distally (Figure 1).

The typical SD curve was non-linear with larger current required to elicit muscle twitch at smaller pulse widths. Figure 2 illustrates an example of SD curves generated for one muscle (supraspinatus) in four separate animals. The consistency of shape and low thresholds indicate the ability to consistently implant and stimulate the motor point across animals.

3D Kinematic analyses confirmed the ability of our stimulation paradigm to produce both single joint and complex multi-joint movements. Figure 3 illustrates single joint movement (elbow flexion) generated by single muscle single muscle stimulation (biceps brachii).

4. DISCUSSION AND CONCLUSIONS

In this work we present initial development of a novel rodent model for FNS-assisted forelimb movement therapy. We were able to identify the motor points of multiple targeted forelimb muscles, successfully implant electrodes, produce consistent isolated joint movements, and produce consistent multi-joint functional forelimb movements. Such a model could enable quantitative investigations of this therapeutic technique and to assess its impact on functional outcomes. The technique may be particularly useful as a means to generate very repeatable movements and to gradually allow the voluntary motor command to take over control of the movement.

References


Acknowledgements

This work was supported in part by HD-040355 and the Bodesign Institute.