Selective Recruitment of Arm Motoneurons in Nonhuman Primates Using Epidural Electrical Stimulation of the Cervical Spinal Cord

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***Abstract*— Recovery of reaching and grasping ability is the priority for people with cervical spinal cord injury (SCI). Epidural electrical stimulation (EES) has shown promising results in improving motor control after SCI in various animal models and in humans. Notably, the application of stimulation bursts with spatiotemporal sequences that reproduce the natural activation of motoneurons restored skilled leg movements in rodent and nonhuman primate models of SCI. Here, we studied whether this conceptual framework could be transferred to the design of cervical EES protocols for the recovery of reaching and grasping in nonhuman primates. We recorded muscle activity during a reaching and grasping task in a macaque monkey and found that this task involves a stereotypical spatiotemporal map of motoneuron activation. We then characterized the specificity of a spinal implant for the delivery of EES to cervical spinal segments in the same animal. Finally, we combined these results to design a simple stimulation protocol that may reproduce natural motoneuron activation and thus facilitate upper limb movements after injury.**

I. Introduction

Recovery of reaching and grasping ability is critical for people suffering from cervical spinal cord injury (SCI). Today, no effective treatment exists for this condition. Systems based on functional electrical stimulation (FES) of the forearm muscles have restored simple hand and arm movements in non-human primates [1] and humans [2,3] with complete paralysis. Nonetheless, control of three-dimensional arm movements underlying daily life activities requires a complex coordination of multiple arm and hand muscles which represents a significant engineering challenge [4]. Moreover, FES recruits muscle fibers in an unnatural order, leading to fatigue and non-natural movement patterns. Therefore, while technically suited to restore fine grasping abilities, it may be unfit to produce smooth and sustained muscle forces required for gravity compensated three-dimensional reaching tasks. Numerous works studied whether intraspinal microstimulation (ISMS) could remedy the limitations of FES. The delivery of micro currents to specific grey-matter sites could activate spinal cord circuitry, which allowed the recruitment of coordinated muscle contractions [5]. Indeed, ISMS trains delivered in the cervical spinal cord elicited functional arm and hand movements in a macaque [6]. These works illustrated the possibility of controlling coordinated movements of multiple muscles through a small number of stimulation channels. However, ISMS has shown limited specificity and highly variable outcomes, especially for the recruitment of extensors muscles in primates [7, 8]. Therefore, the designing of specific stimulation patterns that are needed to elicit a complete coordinated reaching and grasping movement seems daunting. In a different context, epidural electrical stimulation (EES) has shown promising results in improving weight-bearing locomotion and voluntary movements in animal models and in humans with SCI [9-12]. In particular, spatiotemporal alternation of EES bursts have been proven effective in modulating and controlling a broad spectrum of leg movements in rats and nonhuman primates [13-15]. It has been proposed that these protocols, mimicking motoneuron recruitment patterns during movement, exploit dynamic properties of spinal circuits through the modulation of proprioceptive feedback circuits [16], thereby enabling the control of synergistic muscle groups. Moreover, recent results have shown the ability of continuous EES protocols to improve voluntary grasping functions in patients with spinal cord injury [12]. These results open the intriguing possibility to exploit similar stimulation protocols for the recovery of three-dimensional reaching and grasping movements. Here we studied the spatiotemporal patterns of motoneuron activation in the cervical spinal cord during a reach and grasp drawer task [17] in a Macaca Fascicularis. We then characterized the specificity of EES applied at the cervical spinal cord using a customized implant in the same animal during an anesthetized terminal procedure. Finally, we show that natural spatiotemporal patterns of motoneurons activation can be reproduced using a combination of few stimulation sites.

II. Methods

In order to define a spatiotemporal EES strategy, we conducted two experiments. First, we inspected whether a reaching and grasping task would imply a well-defined spatial and temporal pattern of motoneuron activation (Experiment A). Second, we assessed whether it was possible

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978-1-5386-3646-6/18/$31.00 ©2018 IEEE

to selectively recruit groups of functionally activated muscles when delivering EES from a multi active-site epidural electrode (Experiment B). The aim was to combine the results of the experiments A and B to attempt to reproduce the motoneurons activation patterns underlying reaching and grasping movements.

A. Animal and surgical procedures

The experimental protocol was approved by the cantonal (Fribourg) and federal (Swiss) veterinary authorities (authorization No. 2014_42E_FR). Experiments were performed on a female macaque monkey (Mk-CA, Macaca Fascicularis, 12 years, 5.9 Kg). In Experiment A, Mk-CA was trained to perform a reach and grasp drawer task [18-20] while Intramuscular electromyographic (EMG) activity from n=8 muscles was recorded. Experiment B was conducted during a terminal procedure before euthanasia while the animal was kept in deep anaesthesia (induction with ketamine + dormicum + fentanyl, and maintaining with intravenous infusion of propofol). Oxygen supply was provided by means of a nasal tube and heart rate, body temperature and blood oxygenation were continuously monitored throughout.

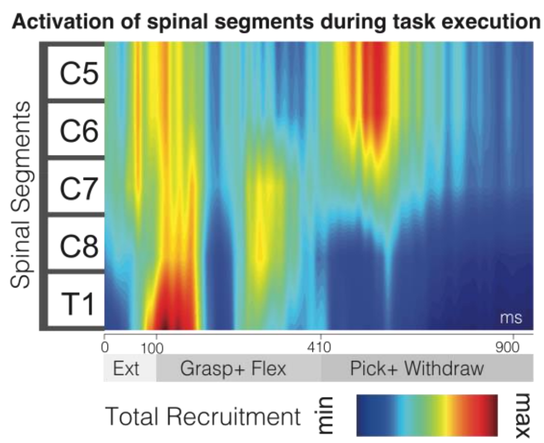

Figure 1. Spatiotemporal motoneurons recruitment map during the execution of a reach and grasp drawer task.The task comprises three phases: an extension (Ext), a grasping + flexion (Grasp+Flex) and the reward picking (Pick + withdraw). The color code shows the level of activation of the moroneurons located in the spinal segments from C5 to T1.

B. Identification of spinal cord activation patterns during movement

We studied the activation patterns of the cervical spinal cord segments during a reach and grasp drawer task in Mk-CA. The behavioral task consisted in the reaching and opening of a drawer, containing a food reward. Mk-CA was trained to rest the hand on a pad while waiting for a starting cue. Once ready, the subject had to single-handedly reach for the drawer knob, open the drawer and pick the reward (food pellet) contained therein. EMG activity was recorded from eight chronically implanted muscles during the repeated execution of the task. We automatically extracted intra-movement phases: the extension phase (from movement onset to drawer handling); grasping/pulling of the drawer until complete opening; and reward picking. We then projected the recorded EMG activity to the anatomical location of the corresponding motoneurons using information extracted from [21] in order to reconstruct the spatiotemporal activation patterns of arm and hand motoneurons during each of these phases (Fig. 1).

C. Electrode specific recruitment curves

A customized spinal implant based on previously reported technology [23] and comprising n=7 independent electrodes was surgically inserted into the epidural space of the cervical spinal cord from an entry point obtained through a laminectomy executed at the vertebral level T1. Single pulse stimulation at different current amplitudes was delivered from each electrode of the spinal implant while intramuscular EMG activity was recorded from n=8 muscles.

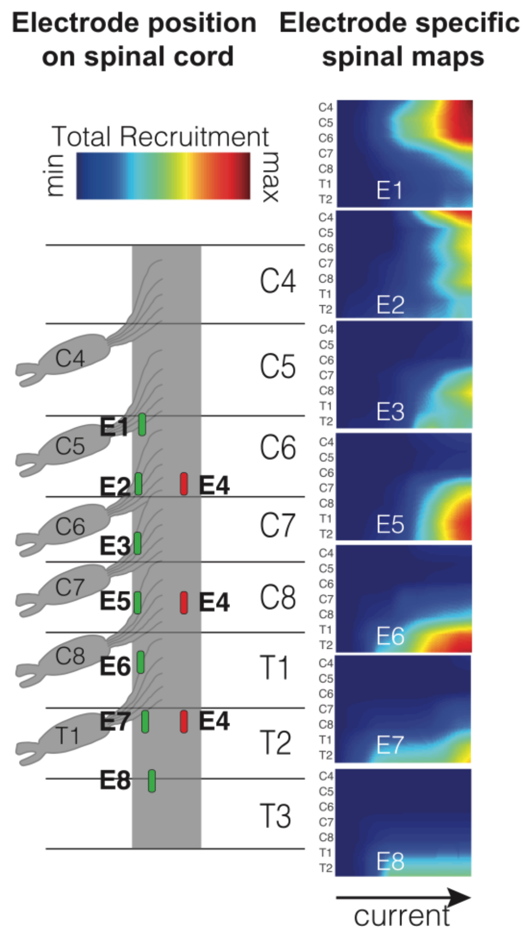

Figure 2. Spatial motoneuron recruitment patterns at increasing stimulation currents, for each stimulation electrode. Active sites are numbered from E1 to E8 and their relative positioning on the spinal cord is shown on the left. E4 comprises 3 shorted electrodes.

In addition, we extracted the spatial pattern of motoneuron recruitment in response to each single pulse of stimulation (Fig. 2). The mapping of the muscles on the spinal cord segments relied on the distribution of motoneurons described in [21]. We then calculated the level of muscle recruitment over the stimulation current amplitudes for each active site separately and we computed recruitment curves. Muscle specificity of i-th muscle was quantified using the selectivity index S_i [22] defined as:

$$S_i = \mu_i - \frac{1}{(m-1)} \sum_{j=1, j \neq i}^{m} \mu_i \qquad (1)$$

where μ_i is the activation level of the i^{th} muscle and m is the total number of muscles.

D. *Design of stimulation protocol*

In order to design an EES strategy that would reproduce the spatiotemporal motoneuron recruitment pattern underlying reaching and grasping movements, we generated time sequences of spatial motoneuron activation patterns elicited by single pulses of EES delivered from the different active sites of the epidural electrode array. Specifically, the active sites and current amplitudes used at the time step were selected as the most suited EES parameters to reproduce the activation level of each segment at this specific moment, as identified from the spatiotemporal map underlying the reach and grasp drawer task.

III. Results

A. *Identification of spinal cord activation patterns during movement (Experiment A)*

The spatiotemporal maps of arm and hand motoneuron activation in the cervical spinal cord during reaching and grasping movements revealed a well-defined pattern of activation over time (Fig. 1, average n=35 repetitions). During the extension phase, the segments that are mainly activated are those innervating the deltoid and triceps muscles (C4 and C5). The transition to the second phase was associated with the activation of extensor hand muscles (innervated in T1) together with flexor muscles of the forearm (innervated at C7). An activation of the T1 spinal segment anticipated the withdraw phase, as the animal was picking the food reward. An activation of the most rostral segments ensued, which was linked to the activation of the deltoid muscle. This activation pattern presented a series of well separated subsequent spinal cord activation hotspots during the task. We concluded that the reach and grasp drawer tasks could be represented by a well-defined temporal pattern of motoneuron recruitment.

B. *Muscle responses induced by cervical EES*

The recruitment curves computed for the different active sites highlighted a good spatial selectivity of the epidural implant. Fig. 2 shows spinal maps reconstructed for all the electrodes, associated to their position on the spinal cord. Each stimulation site activates preferentially the spinal segments that are located in close proximity. Fig. 3 shows muscle recruitment curves and selectivity indices of the active sites E1, E2 and E6. These three active sites enabled the selective activation of arm/hand flexors, arm/hand extensors and digit muscles, respectively. We conclude that EES of the cervical spinal cord may be able to access specific groups of functionally activated muscles.

C. *Design of stimulation protocols*

Fig. 4 shows a reconstructed spatiotemporal map elaborated from the single pulse spatial motoneuron responses. We combined responses from three electrodes (E1, E2 and E6) to produce an artificial spatiotemporal motoneuron activation map that matched the one measured during movement. The resulting map showed a succession of spatially defined hotspots that were qualitatively similar to those found in the task-specific map. Pearson's correlation coefficient between the original and reconstructed map equals 0.64.

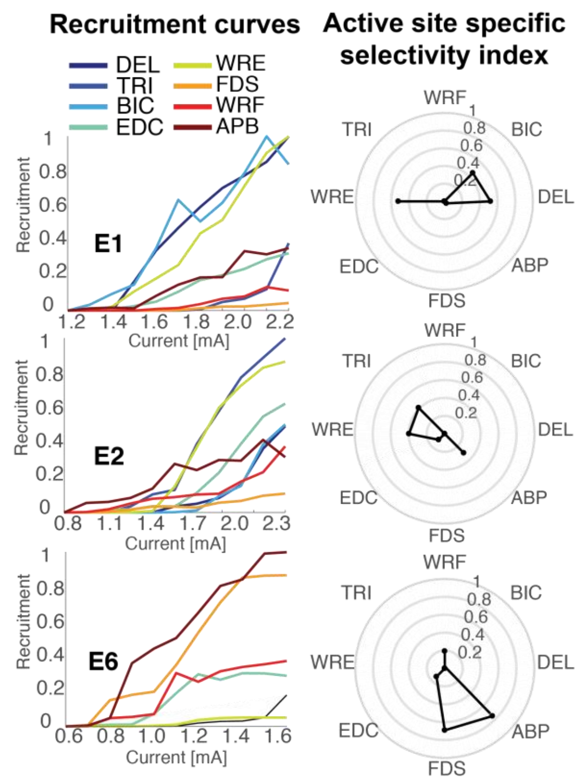

Figure 3. Recruitment curves and selectivity indexes are shown for all the muscles and for the three epidural electrode active sites E1, E2 and E6 (from top to bottom). Muscles shown: deltoid (DEL), biceps (BIC), triceps (TRI), extensor digitorium communis (EDC), wrist extensor (WRE), flexor digitorium superficialis (FDS), wrist flexor (WRF), abductor pollicis brevis (APB).

IV. Conclusions

In this study we inspected whether a reach and grasp drawer task implies a well-defined spatial and temporal pattern of motoneuron activation. Successively, we assessed whether it was possible to selectively recruit groups of synergistic muscles when delivering EES from a multi-electrode array epidural electrode with the aim of reproducing the motoneurons activation patterns underlying reaching and grasping movements. The reproduced activation map qualitatively matched spatiotemporal map measured during the execution of the task (Fig. 4). Therefore, we concluded that it is possible to define selective EES protocols of the cervical spinal cord reproducing coordinated activation of arm and hand muscles during functional reaching and grasping movements in nonhuman primates. These combined results show encouraging data for the design of selective EES stimulation protocols for improving upper limb function in people with tetraplegia.

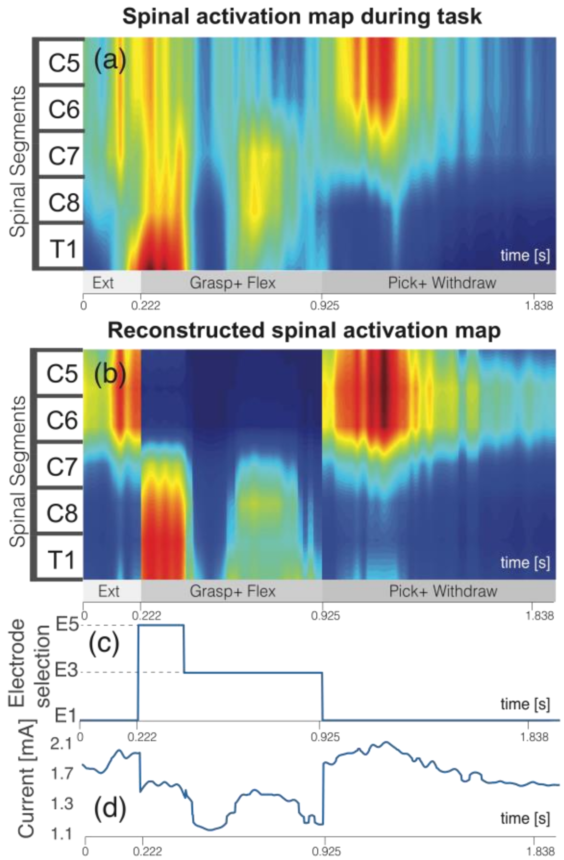

Figure 4. The task-specific spatiotemporal activation was reproduced selecting the spinal segments activation obtained from single pulse EES delivered from 3 electrodes. Current amplitudes were chosen to mimic at best the activation pattern obtained during the task. From top to bottom: (a) the original activation map represents the activation of the spinal segments from C5 to T1; (b) the reconstructed activation map shows the activation of the spinal segments that would be induced by the stimulation delivered from 3 electrodes; (c) the curve shows which active sites are selected over time during the task to reproduce the spinal activation map; (d) the curve indicates the amplitude of the stimulation current for the chosen electrode over time.

ACKNOWLEDGMENTS

This work is supported by: a grant from the Wings for Life to M.C. the Ambizione program of the Swiss National Science Foundation (SNSF) to M.C., the NCCR Robotics of the SNSF, the University of Fribourg and the Wyss Center for Bio and Neuro Engineering; the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska- Curie grant agreement No. 665667, and an Industrial Grant-Agreement between GTX Medical and the University of Fribourg and EPFL.

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