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Strokes and traumatic spinal cord and brain injury

RECOVERY OF ARM AND HAND MOVEMENTS IN PATIENTS WITH CERVICAL SPINAL CORD INJURY USING ELECTRICAL SPINAL NEUROMODULATION/STIMULATION ASSISTED WITH AN ARM EXOSKELETON

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1. Project summary

The mobility of the arms and hands is essential to carry out the vast majority of daily activities, ranging from object manipulation to non-verbal communication. Damage to the neural circuits that control the upper extremities inflicts devastating consequences, drastically restricting the lifestyle of the patient, who becomes dependent on support devices, greatly reducing his or her autonomy and freedom.

The severity of the injuries and the lack of reliable treatments mean that the impairments associated with SCI persist throughout life. In fact, among all the pathological symptoms developed, patients have placed a high priority on finding therapies to restore manual function.

In the last decade several therapeutic interventions, e.g. cell transplants, the blockade of inhibitory molecules, digestion/blockade, motor training, and the action of pharmacological agents have been shown to successfully promote the regeneration of spinal cord axons and to allow functional restoration to a certain extent. Unfortunately, most of these studies have shown very good results in preclinical models, but with little efficacy when applied to spinal cord patients.

An alternative strategy to axonal regeneration and tissue remodeling is the use of neural prosthetic technology or modulation of the central nervous system through the release of electrical current that modulates the activity and plastic changes of the circuits.

Spinal cord neuromodulation has emerged as a potential strategy to promote functional recovery. The delivery of electrical current to the CNS can strengthen and facilitate the functionality of the residual connectivity, increasing the excitability and intrinsic plasticity of the conserved connections between the brain and the spinal cord. Also, recently developed neural prosthetic technologies are breaking new ground with promising implications in neuroscience. Signal decoding allows patients to control assistive devices

2. Results

Objective 1: To develop an autonomous hybrid robotic system to conduct the rehabilitation of arm and hand movements in the spinal column in spinal cord injured patients. PI; Juan Moreno, CSIC

At the CSIC, work has been done on the development of hybrid robotic systems, which combine the advantages of using electrical stimulation with artificially generated movement through the innervation of the natural motor pathway and the benefits of robotic exoskeletons to automate the execution of repetitive rehabilitation exercises. The hybrid robotic system focuses on helping users move their paretic arm to different directions in space. This proposed rehabilitation platform can be seen as an autonomous tool in which several subsystems are integrated. These subsystems collaborate with each other to cooperatively carry out the rehabilitation task.

The work has focused on integrating the different components that make up the hybrid robotic system in a single platform for the rehabilitation of the motor function of the upper limb. The equipment consists of the hybrid assistive device (upper limb exoskeleton + stimulator device), a high-level controller (HLC), neuromodulation system, user interface (including visual feedback), and a new neuromuscular assessment tool. In addition, different control strategies have been implemented to automatically establish the optimal stimulation parameters. Two types of studies were performed to continue the development of detailed evaluation of muscle function based on high-density EMG recordings: 1) analysis of muscle fatigue in the tibialis anterior muscle (characterization study with intact users) and 2) evaluation of spasticity using HD-EMG (in a clinical setting under a robotics-based rehabilitation scenario). Lastly, methods have been developed to facilitate optimal timed assistance according to the user's own intention to move to promote plasticity and maximize result of rehabilitation. The CSIC has completed work to optimize the detailed assessment of muscle function based on high-density EMG recordings that is required during robotic rehabilitation to determine the activation properties of motor units that can be used to monitor and control muscle function intervention.

Objective 2: To determine whether concomitant transcutaneous electrical stimulation of the cervical spinal cord to arm, with arm exoskeleton-assisted hand rehabilitation facilitates recovery of arm and hand function in patients

with traumatic cervical spinal cord injuries. PI; Jesus Benito, Guttman Institute

At the Guttman Institute of Neurorehabilitation, the excitability of the cervical circuits that control the muscles of the arms when receiving periods of transcutaneous electrical stimulation of the cervical spinal cord was evaluated in healthy subjects and in spinal cord patients.

In studies on healthy subjects, the patterns of transcutaneous stimulation were characterized, specifically those that control the intensity of stimulation and the degree of muscular activation of the exercise that develops concomitantly with the stimulation. We have shown that both a stimulation intensity with sub-threshold values for motor activation and the concomitant higher degree of muscular activity favor a higher degree of excitability of the medullary circuitry, evaluated by means of electrophysiological tests. In conclusion, these studies have allowed us to optimize a pattern of transcutaneous stimulation to increase the excitability of the spinal cord circuits, and to be used as a model of spinal cord neuromodulatory rehabilitation in patients with spinal cord injury.

In spinal cord patients with incomplete cervical injury, the control of an arm exoskeleton (Armeo) were evaluated when only rehabilitation of the exoskeleton is received, or instead, when it is accompanied by a pattern of stimulation. The results indicate that the patients subjected to neuromodulatory rehabilitation obtained a better response in the components of some movements compared to the subjects with classical rehabilitation.

Objective 3: To identify the cellular and molecular changes in the cerebrospinal connectome that mediate grasp reach and recovery in cervical spinal cord injured rats receiving cervical electrical stimulation. PI; Guillermo García, Institute of Neurosciences-UAB

The work was aimed at identifying the brain regions as well as the cellular changes in their neural circuits involved in the use of the arm and hand to grasp objects. Rodents were used so that once they had learned the manual task, electrophysiology and histology studies could be carried out.

Through the study of the c-fos activity marker, healthy animals allowed mapping of the regions where the highest density of c-fos positive cells that are activated when the animal performs the grasping task is concentrated. Preliminary results show, first, that the pattern of c-fos activation is much more complex than that required to activate lumbar circuits during locomotion. We have shown that over different periods of time after learning the number of c-fos neurons is much lower than when compared to those expressed during locomotion. A first analysis suggests a location mainly in the dorsal horns and in the intermediate zone of the medullary gray matter. Positive c-fos neurons have been visualized in all segments of the cervical cord.

We are using two approaches to assess corticospinal connectivity. Firstly, studying the evoked potentials, recording the electrical activity of the muscles of the forelegs when stimulating the motor cortex of the contralateral hemisphere. In rodents without anesthesia and with implanted recording and stimulation electrode systems, we have recorded cortical potentials in proximal and distal muscles of the forelimbs, and identified groups of signals with different latencies that correspond to the activation of different structures of the forelimb corticospinal pathway. This classification of the signals will make it possible to identify the selective plasticity of the descending pathways.

Second, the distribution of cortical neurons that project their axons to the cervical segments has been analysed anatomically. Through AI algorithms, a motor representation map was reconstructed in 2D and the extension and occupation within the cerebral cortex that the cortico-cervical neurons possess has been described.

3. Relevance and possible future implications

Recently, independent research groups in Switzerland and the United States have shown unprecedented results, in which electrical stimulation of the lumbar spinal cord has enabled patients with spinal cord injury to regain the ability to maintain posture and walk. Researchers have found that neuromodulation of afferent sensory fibers activates spinal circuits that control locomotion and posture, allowing spinal patients to perform these movements while receiving stimulation simultaneously. The great challenge will be to design devices that can activate neuromodulation based on the intrinsic will of the subject and not from external activation controllers, and thus not having to depend on any external controller. Another great challenge in which the consortium is immersed will be to show whether the cervical spinal cord has neuronal networks as powerful as those present in the lumbar spinal cord for walking, which, when receiving electrical stimulation, are capable of evoking complex movements with the arms and/or in incomplete lesions, and that their activity is efficient enough to facilitate the movements of the arms and hands.

The results obtained by the different groups of the consortium point to the suitability of cervical neuromodulation to facilitate the function of cervical circuits to develop tasks that require fine motor control of the arms and hands and suggest the need to develop intrinsic control systems that allow a fine neuromodulation of the different regions of the cervical spinal cord to perform parts of the specific movements. This milestone will be achieved when an exhaustive knowledge of the functional structure of spinal circuits and the development of technology to record and decode signals to control stimulation systems is achieved.

4. Scientific Publications

Giovanni Corvini, Ales Holobar, Juan C. Moreno. On Repeatability of MU Fatiguing in Low-Level Sustained Isometric Contractions of Tibialis Anterior Muscle. Proceedings: ICNR 2020:, Part of the Biosystems & Biorobotics book series (BIOSYROB, volume 28). Converging Clinical and Engineering Research on Neurorehabilitation IV pp 909–913.

Kumru H, Flores A, Rodríguez-Cañón M, Soriano I, García L, Vidal-Samsó J. Non-invasive brain and spinal cord stimulation for motor and functional recovery after a spinal cord injury. Rev Neurol. 2020; 70(12): 461-477.

Kumru H, Flores A, Rodríguez-Cañón M, Edgerton VR, García L, Benito J, García-Alías G, Vidal J. Cervical electrical neuromodulation effectively enhances hand function in healthy subjects by engaging a use-dependent intervention. Journal of Clinical Medicine. 2021; 10(2): 195.

Castillo-Escario Y, Kumru H, Vidal J, Jané R. Assessment of Trunk Flexion in Arm Reaching Tasks with Electromyography and Smartphone Accelerometry in Healthy Human Subjects. Scientific reports. 2021; 11(1).

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Hatice Kumru, María Rodríguez-Cañon, Victor R. Edgerton, Loreto García, Africa Flores, Ignasi Soriano, Eloy Opisso, Yury P. Gerasimenko, Xavier Navarro, Guillermo García Alias, Joan Vidal. Transcutaneous Electrical Neuromodulation of the Cervical Spinal Cord Depends Both on the Stimulation Intensity and the Degree of Voluntary Activity for Training. Journal of Clinical Medicine. 2021; 10(15): 32-78.

Flores Á, López-Santos D & Garcia Alias, G. When spinal neuromodulation meets sensorimotor rehabilitation: Lessons learned from animal models to regain manual dexterity after a spinal cord injury. Frontiers in Rehabilitation Sciences, 94.

Doctoral Theses

Loreto Garcia. Impact of noninvasive electrical neuromodulation of the spinal cord on the functionality and quality of life of people with cervical spinal cord injury. Directors: Jesús Benito Penalva and Joseo Medina Casanova. Institut Guttmann-UAB. (defense date September 2022)

Diego Lopez. Neuromodulation of the cervical spinal cord to recover the reaching and grasping movement in rats with cervical spinal cord injury. Directors: Guillermo García and Africa Flores. Autonomous University of Barcelona. (defense date July 2023)

Master's theses

Giovanni Corvini Analysis of conduction velocity from High-Density surface EMG as indicator of muscle fatigue during robot-mediated ankle movements. Director: Cincotti, Febo. Co-director: Moreno, Juan C. Master's Thesis (Corso di Laurea Magistrale in Artificial intelligence and Robotics). Department of Automatic and Management Computer Engineering, University of Rome. July 2019. 2019.

Marina Albaba. Analysis of muscle activation patterns during bilateral isometric contractions. Directors: Juan Camilo Moreno Sastoque, Lucia Prensa Sepúlveda. Master in Neuroscience. Science Faculty. Autonomous University of Madrid. September 2021 – present.

Eve Martinez. Deciphering the architecture of the spinal networks involved in task specific motor control. Director: Guillermo Garcia. Master in Neuroscience. Autonomous University of Barcelona, June 2019.

Andrea Diaz. Determining the role of the corticospinal and reticulospinal pathways in hand function. Director: Guillermo Garcia. Master Neuroscience. Autonomous University of Barcelona, September 2019.

Pau Lucena: Analysis of corticomotor evoked potentials in the upper limbs of anesthetized rats. Directors: Guillermo García and Raimon Jané. Master in Biomedical Engineering. Technical School of Industrial Engineering of Barcelona. Polytechnic University of Catalonia, February 2022

Adrià Alsina: An image processing approach for corticospinal neuron mapping. Directors: Guillermo García and Mercè Vall-llosera. Master in advanced telecommunications technologies. Technical School of Telecommunications Engineering of Barcelona, Polytechnic University of Catalonia, February 2022

Dario Toria, How the context of a movement influences manual dexterity. Director: Guillermo Garcia. Master in Neuroscience. Autonomous University of Barcelona, 2021

Carla Guixé Sendiu. Effects of transcutaneous spinal cord stimulation on excitability and spasticity after spinal cord injury: Effects of a single session. Director: Dr. Hatice Kumru. Master in Neuro-engineering of Neurorehabilitation. Institut Guttmann-UAB. July 2021

Ricard Jubany. Transcutaneous neurostimulation for neuropathic pain in spinal cord injuries. Director: Dr. Hatice Kumru. Master Neurorehabilitation Institut Guttmann-UAB. July 2021

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Roger Rifa. Effect of transcutaneous stimulation on gait reduction in patients with spinal cord injury. Director: Dr. Hatice Kumru. Master Neurorehabilitation Institut Guttmann-UAB. July 2021