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● PERSPECTIVE

Motor neuroprosthesis for injured spinal cord: who is an ideal candidate?

A spinal cord injury (SCI) shatters people's lives in a fraction of a second, leaving them paralyzed, often for the rest of their lives. The devastation caused by SCI is significant around the world. Though the exact prevalence of the injury is unknown, according to recent statistics, the number of injuries is estimated to be between 1.65 and 7.06 million worldwide (Alam and He, 2014). A recent report from the World Health Organization (WHO) states that, every year, 250,000–500,000 new spinal cord injuries occur around the world (Bickenbach et al., 2013). Beyond the physical sufferings of these paralyzed individuals, SCI has huge economic and social impacts. In the United States alone, the average lifetime cost for a young adult at an age of 25 with high quadriplegia is US$4.6 million and with paraplegia is US$2.3 million (according to the National Spinal Cord Injury Statistics Center, USA). At the same time, in Australia, the average lifetime cost is estimated to be AU$9.5 million for a quadriplegic and AU$5 million for a paraplegic (according to Access Economics, Australia). The actual cost of care for patients with SCI in China and India, the two most populous countries in the world, with probably the highest incidences of SCI, is, however, unknown.

Currently, there is no known cure for paralyzed patients suffering from severe SCI (Silva et al., 2014). Hence, ongoing research is searching for an effective treatment modality to cure the injured spinal cord and treat the associated complications arising from the injury. There are three main streams of research on SCI recovery: neuroprotective to stop further damage immediately following an injury; neuroregenerative to reconnect the broken spinal cord; and neuroengineering to utilize the available neural circuits to restore function (Guan and Hawryluk, 2016). While neuroprotective and neuroregenerative studies have shown positive results in animals, till now, they are still in their very early stage of translation to human subjects. In contrast, in recent years, central nervous system-based motor neuroprosthesis (MNP) has resulted in successful restoration of lost motor functions in patients with complete spinal cord injuries, and thus hold great promise in SCI rehabilitation.

MNP is an engineering approach to bypass the injury site of the spinal cord to activate the functional circuit below the injury to restore the lost functions of a patient with severe paralysis resulting from a SCI. This technology holds great promise for SCI rehabilitation. In recent years, different laboratories around the world have demonstrated the feasibility of using this technological approach to restore motor functions in paralyzed patients. Cortical MNP uses direct neural recording from the brain, decodes the patient's movement intentions using advanced signal processing algorithms, and uses artificial means for movements *via* actuators or direct stimulation of the paretic limbs. There are both invasive and non-invasive approaches to record brain signals for cortical MNP. Until now, the most successful cortical MNP is invasive (Alam et al., 2016), and requires a craniotomy to implant a microelectrode array into the motor cortex area to record the patient's motor-related cognitive activities. Hochberg et al. (2006) were the first to conduct a successful human trial of such cortical MNP, called BrainGate. Using the cortical MNP system, a quadriplegic patient was able to control a specially programmed computer cursor, open and type emails, and remotely operate a television, just by thinking. Harkema et al. (2011) demonstrated a new modality, spinal MNP, by implanting stimulating electrodes in the dorsal epidural space of the spinal cord, posterior to the injury site to restore full-weight bearing standing and assisted stepping in a paraplegic patient with motor-complete SCI. More strikingly, after seven months of training with this novel spinal MNP, the patient regained supraspinal control of some leg muscles (Harkema et al., 2011).

As cortical and spinal MNPs are gaining in maturity, a question emerges: can all SCI patients benefit from this technology? In this article, we provide our perspectives on the potential users of this innovative technology.

SCI has different severities, complete or incomplete, and occurs at different spinal levels, from cervical to thoracic and lumbosacral, resulting in quadriplegia or paraplegia. Since patients with incomplete SCI can benefit from extensive physical rehabilitation training, MNP is potentially viable for motor-complete SCI patients as they have no sensorimotor function left below the injury level. Quadriplegics with motor-complete SCI would likely benefit from cortical MNP as they retain no or very few upper-limb functions after their injury. These patients are often fully dependent on their caregivers for their daily activities. One major challenge for implementing MNP for quadriplegics is controlling body balance, needed to enable standing and walking. As motor-complete quadriplegics have no upper-limb and postural control, it is very unlikely that these patients could use any existing decoding algorithm of MNP for independent standing and stepping. Still, such a person can use cortical MNP to control an external device or his/her own paretic upper limb through functional electrical stimulation (FES) of muscles or peripheral nerves to restore movement. Volitional control of paretic hands by using such cortical MNP has recently been demonstrated (Bouton et al., 2016; Ajiboye et al., 2017). In both studies, neural signals were collected using intracortical microelectrodes from the hand area of the motor cortex of patients with chronic cervical SCI. Advanced neural decoding algorithms were utilized to decode movement intention into usable commands to trigger a multichannel neuromuscular electrical stimulator. The electrical stimulation activates the selected muscles of the paretic arm to induce different grasps. These proof-of-concept studies essentially developed a bypass across the spinal cord lesion and demonstrated the potential of cortical MNP in restoring motor function in SCI quadriplegics.

It is not clear whether SCI paraplegics could benefit from the cortical MNP technology to the same degree as quadriplegics. As paraplegics still have fully functional upper limbs, cortical MNP might be a less likely option. Furthermore, the requirement of an invasive procedure to implant an electrode array into the brain needs to be justified by potential functional gains. Perhaps a spinal MNP controlled by a handheld control device or a processor that interprets the patient's commands can be more beneficial for restoring lower limb functions in SCI paraplegics. A spinal MNP primarily activates the central pattern generator (CPG) of the spinal cord. CPG is composed of a specialized neural circuit capable of generating rhythmic activities essential for walking. In spinally intact persons, walking requires no or little visual feedback as the leg movements are adjusted in time and space through a local proprioceptive circuit in the lumbosacral region of the spinal cord (Rossignol et al., 2006). Provided that this feedback loop is intact below the injury site in a SCI paraplegic patient, it would be extremely beneficial to use this loop along with the CPG to enable locomotor function. Recent clinical studies on SCI paraplegics indicate that simply activating these spinal neural circuits is enough to not only restore standing and stepping functions but also to regain volitional control of paretic legs (Angeli et al., 2014; Grahn et al., 2017). After several years of using this novel spinal MNP, a patient improved other functions including blood pressure control, body temperature regulation, bladder control, sexual function, and also regained some sensation even without the system being turned on (Angeli et al., 2014). It is expected that, with additional kinematic sensors connected to the lower limbs and trunk, the spinal MNP may work more efficiently in a closed-loop manner to restore natural walking. Furthermore, with robust decoding and encoding algorithms, spinal MNP might become a viable clinical solution for SCI paraplegics.

Based on the above discussion, we would like to suggest that the ideal candidates for cortical MNP would be motor-complete SCI quadriplegics, whereas the ideal candidates for spinal MNP would be motor-complete SCI paraplegics. However, several challenges still remain before cortical and spinal MNPs can be clinically used to restore functional independence in these SCI patients. Developing a minimally invasive wireless cortical recording system with long-term biocompatibility with brain tissue is among the most desirable outcomes for future cortical-MNP research. Wireless power is another major challenge for implantable devices, especially for neurostimulators, as they require a continuous power supply for functional stimulation. Without wireless power transfer, spinal-MNP will face serious challenges as typical stimulators require battery replacements within 2–5 years of implantation. Radio frequency (RF) power transfer may not be safe as it can generate a large current by induction. Having such inductive coil inside the body may increase the risk of hacking. Restoration of sensory function is another major challenge of neuroprosthetics research. It is believed that closing the loop *via* sensory feedback will not only restore the lost sensation of these patients, but will also improve the motor functions of cortical and spinal MNPs.

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