CNS Neuroscience & Therapeutics

EDITORIAL COMMENTARY

The Spark of Life: Engaging the Cortico-Truncoreticulo-Propriospinal Pathway by Electrical Stimulation

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doi: 10.1111/cns.12520

Cephalosomatic anastomosis (HEAVEN/AHBR) is enabled by the GEMINI spinal cord fusion protocol [1,2]. This hinges on two pillars: the possibility to refuse a certain number of axons of the severed cords by way of substances called fusogens [1–3] and, more importantly, on the reconnection of the cortico-truncoreticulo-propriospinal (CTRPS) pathway, a sensorimotor highway that links the motor cortical areas to the spinal motor neurons via the brainstem reticular formation and spinal propriospinal neurons (or interneurons) [2,4]. As explained [1,2], a very sharp severance ensures virtual sparing of the gray matter at the point of section, so that cells on both sides of the fusion interface can reextend [resprout] their axons and reestablish continuity.

To accelerate this process of reconnection, electrical stimulation at the interface will be delivered via an implanted, peridural multichannel paddle.

Targeting Central Pattern Generators

As highlighted by Minassian and Hofstoetter (this issue), spinal cord stimulation (SCS) has been employed for the rehabilitation of spinal cord injury (other than pain) for more than 20 years, but never gained the popularity it deserved, except among a few interested groups. This is now changing, and clinicians are slowly catching on. SCS achieves the goal of reengaging lost movements by tapping into the cortico-truncoreticulo-propriospinal pathway (CTPRS) pathway that links the so-called cervical and lumbar motor central pattern generators (CPG). Minassian and Hofstoetter discuss the lumbar CPG, namely the lumbar locomotor network that plays an essential role in the generation of locomotor outputs, and how SCS can reengage it and restore some degree of clinically useful motor activity in the lower limbs. Actually, humans also likely possess a cervical CPG, which controls the upper limbs. Both CPGs display facilitatory interlimb neural coupling via propriospinal connections, as in quadrupedal animals [5,6]. Importantly, voluntary rhythmic arm movements increase leg muscle recruitment during submaximal recumbent stepping [7], modulate leg muscle activity during standing [8], and can even evoke stepping-like leg movements [9]. Solopova et al. [10] have shown that peripheral sensory stimulation (continuous muscle vibration) and central tonic activation (postcontraction state of neuronal networks following a long-lasting isometric voluntary effort, that is, Kohnstamm phenomenon) can evoke nonvoluntary rhythmic arm movements in human subjects, but also nonvoluntary rhythmic arm movements together with rhythmic movements of legs. This is evidence of the rhythmogenic capacity of cervical neuronal circuitries.

As mentioned, in the cephalosomatic anastomosis (CSA) (HEAVEN/AHBR) setting, SCS will be applied cervically, straddling the point of fusion. The electrical stimulation will drive both CPGs and engage the CTRPS path [1,2,4]. Of course, if necessary, a percutaneous or neurosurgical lumbar electrode can be added at a later time.

Accelerating Sprouting

An equally important role of electricity will be to accelerate the sprouting of the severed CTPRS pathway. Animal (rat) studies show how electrical stimulation of the primary motor cortex (M1) after unilateral pyramidotomy increases corticospinal tract (CST) axon length, strengthens spinal connections, and restores forelimb function. In particular, M1 electrical stimulation promotes increases in corticofugal axon length to multiple M1 targets, including the brainstem and spinal gray matter [11]. In rats submitted to pyramidotomy, daily application of combined M1 intermittent theta burst stimulation (iTBS), a form of cortical stimulation, and cathodal (but not anodal) trans-spinal transcranial direct current stimulation (tDCS) targeted to the cervical enlargement (15 × 20 mm surface electrode, one pole over cervical cord, the other over the chest, 10-day-long stimulation, 27 min/day) significantly restored skilled movements during horizontal ladder walking. Stimulation produced a 5.4-fold increase in spared ipsilateral CST terminations [12].

The ability of invasive extradural (neurosurgical) and noninvasive cortical stimulation to promote neural plasticity is well known and has clinical applications, for example, for stroke and neural injury rehabilitation [see 13,14 for review]. The above protocol can be easily adapted to the CSA protocol to speed up motor recovery. However, instead of applying a neurosurgical paddle on M1 that adds to the onus of the surgery, the patient will be stimulated concomitantly via daily applications of transcranial magnetic stimulation to M1 and cervical SCS.

In similar work [15], corticospinal volleys evoked by M1-centered TMS were timed to arrive at corticospinal–motoneuronal synapses prior to antidromic potentials evoked in spinal motoneurones by external electrical brachial plexus stimulation (cathode in the supraclavicular fossa, anode over acromion) (pairing): 100-pair conditioning (100-PCMS) was more efficacious than 50-PCMS, both as single and spaced conditioning (2 blocks of 50, 15-min break), with an hour-long after-effect. This protocol too can be easily integrated to induce spinal plasticity and enhance corticospinal transmission. Importantly, the effect is due to both an effect on the direct corticospinal synapse and the CTRPS pathway [16].

Concluding Remarks

Electricity holds great potential in supporting motor recovery in a head transplant. Of course rehabilitation after a head transplant can be supplemented by other means. For instance, Gerasimenko et al. [17] reported recovery of voluntary movement in 5 cervical or thoracic motor-complete (AIS B) patients by combining TENS (2.5-cm-round cathode manually kept on the skin between spinous processes T11-2 or coccyx and two 5.0 × 10.2 cm^2 rectangular plates placed symmetrically on the skin over the iliac crests as anodes; monopolar rectangular stimuli (1-ms duration) filled with a carrier frequency of 10 kHz and at an intensity ranging from 80 to 180 mA, 30 Hz at T11 and 5 Hz at Co) and buspirone 7.5 mg orally twice daily for 4 weeks (plus training) [see also 18 and 19]. Hayes et al. [20] reported that transient hypoxia (5, 90-second hypoxic exposures (dAIH, fraction of inspired oxygen [Fio2] = 0.09) on five consecutive days), along with overground walking training 1 hour later, improved walking speed and endurance after incomplete spinal cord injury.

Recently, a Japanese group proposed deep brain stimulation of the nucleus accumbens to enhance "motivation" (will-power) in spinally injured patients [21], but this technology is invasive and will not be incorporated. Instead, cortical stimulation in its noninvasive modality will be tapped into, as noted [13,14].

It is most fitting that electricity was the "engine of creation" in Mary Shelley's Frankenstein novel, as Victor Frankenstein recalled:

> . . .when I was fifteen years old. . .we witnessed a most violent and terrible thunderstorm. . .before this I was not unacquainted with the more obvious laws of electricity. On this occasion a man of great research. . .entered on the explanation of a theory which he had formed on the subject of electricity and galvanism, which was at once new and astonishing to me. . .[p33]

Two centuries later, electricity is about to give life again [22,23].

Conflict of Interest

The authors declare no conflict of interest.

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