Enabling motor control in chronic spinal cord injury: found in translation

Chronic spinal cord injury affects between 440 and 681 people in every million, depending on country (Bickenbach, 2013), and remains an unmet medical need. While there has been an exponential increase in our molecular and cellular understanding of spinal cord injury over the last three decades, with a considerable number of interventions producing functional neurological recovery in experimental models, not one has been translated into an FDA-approved treatment available in the clinic. Translating neurological concepts from basic neuroscience to clinical treatments is one of the toughest challenges and its success depends on a bidirectional dialogue (Curt, 2012). In the current issue of Brain, Susan Harkema and Victor Edgerton scale up the results of an earlier case report (Harkema et al., 2011) to demonstrate that epidural stimulation, beginning >2 years after spinal cord injury, can restore voluntary movement in a select group of patients (Angeli et al., 2014).

Epidural stimulation (25 or 30 Hz, 1.5–2.5 V) was applied to the index patient from the initial case report and to three additional patients (neurological lesion level C7–T5), via an implanted device at spinal cord level L1-S1 as previously described (Harkema et al., 2011). Two of the patients had lesions classified as grade A according to the American Spinal Injury Association Impairment Scale (AIS) (sensory and motor complete), while two had lesions classified as AIS B (sensory incomplete). The concept of lumbar stimulation to treat spinal injury is derived from research in the ‘spinal cat’ that revealed the presence of a locomotor centre in the lumbar spinal cord (Grillner et al., 1969), a discovery that was further advanced in human patients by Milan Dimitrijevic. It was subsequently confirmed that both propriospinal and supraspinal afferents to spinal locomotor centres could facilitate motor output in patients with complete spinal cord injury (for review see Dietz and Fouad, 2014). The concept of enhancing supraspinal input to reach lumbar locomotion centres now receives clinical support from the extended ‘proof of principle’ study of Angeli et al. (2014). Indeed, this pilot study might represent one of very few examples of successful translation: ‘found in translation’.

Although there are occasional late conversions after chronic spinal cord injury from ‘motor-complete’ to ‘motor-incomplete’ (Kirshblum et al., 2004), these are rare and chronic spinal cord injury is generally considered a neurologically stable condition. In contrast, patients in the current study regained volitional control of paralyzed leg muscles upon epidural stimulation, and became able to stand. The externally applied electrical field caused...
excitation of motor circuits (spinal ‘motor pool activation’), allowing coordinated flexor- and extensor muscle activation, as indicated by reciprocal EMG activity (Fig. 1). Voluntary movements, which were initially dependent on epidural stimulation, eventually became possible without stimulation. To verify that the movements were indeed voluntary in origin, patients were instructed to vary the timing of movements as well as muscle force in response to visual and auditory cues.

Within this highly selected subgroup there was a 100% response to treatment, albeit in a non-uniform manner as exemplified by differences in stimulation intensity thresholds across individuals and in the recovery of EMG patterns. Electrophysiological measures confirmed that, with epidural stimulation, EMG activity during voluntary movement was regained in the intercostal muscles innervated by the sixth thoracic segment (Th6), as well as in the tibialis anterior (L4), extensor digitorum longus (L5), and extensor hallucis longus (L5), muscles. A reduced and infrequent EMG response was observed in the soleus muscle (S1). By contrast, there was no return of motor evoked potentials elicited by transcranial magnetic stimulation in tibialis anterior or soleus. This confirmed that activation and remodelling of spinal interneuron circuitry is the main effector mechanism, as no improvement in direct corticospinal tract signal could be detected (Fig. 1). Analysis of sensory function by means of somatosensory evoked potentials

Figure 1  Epidural stimulation contributes to volitional motor control in patients with chronic motor-complete spinal cord injury. (A) Residual supraspinal motor efferent tracts are unable to elicit volitional movements, as confirmed by the absence of motor evoked potentials. (B) The electromagnetic field generated by epidural electrical stimulation (ES) shifts the excitation level of remaining ‘silent’ supraspinal inputs, which leads to the activation of spinal ‘motor pools’. This effect can be observed immediately after a single stimulation in pre-trained ‘discomplete’ subjects. (C) The formation of ‘relays’ between supraspinal efferents (including the corticospinal tract) and propriospinal neurons may further contribute to recovery of function. (D) Stimulation of propriospinal (sensory) afferents is a prerequisite for the effects on locomotion mentioned above. (E) The restoration of motor control was confirmed by the phase-specific EMG recovery pattern seen in flexor and extensor muscles. DRG = dorsal root ganglion; f = flexor muscle; e = extensor muscle; p = propriospinal neuron. Modified from Rossignol and Frigon (2011).
revealed shorter latencies in two patients (50%), implying a ‘neurorestorative’ effect. It appears that classical electrophysiological measures are sensitive tools for monitoring the extent of injury to the spinal cord but are less sensitive to motor recovery and regeneration. Hence, this study emphasizes the need for sensitive electrophysiological methods that can trace the discrete but significant post-injury remodelling of spinal short circuit connectivity that may allow for voluntary movement.

In the first experimental session, three of the four motor complete patients were already able to generate voluntary EMG activity in the presence of epidural stimulation. These patients are likely to be characterized by residual ‘silent’ descending input to the spinal circuitry: a state referred to as ‘discomplete’. This ‘discompleteness’ is backed up by the ability of these patients to support 44% of their body weight during pre-implantation treadmill training. The one patient who did not respond immediately did gain voluntary motor control with a 7-month latency after combined epidural stimulation and rehabilitation therapy. In this patient, remodelling of lumbosacral interneuron plasticity might have been required in addition to the delayed conversion of remaining ‘silent’ supraspinal input (Fig. 1). In all patients, voluntary leg movements after epidural stimulation were characterized by a delay in the motor response after the intention to move. This suggests integration of indirect ‘detour’ pathways, including rostro-caudal signal propagation by propriospinal interneurons (Fig. 1) (Courtine et al., 2008).

Inevitably, several questions remain unanswered. One relates to the specificity of the stimulation with respect to the neurons whose activity is altered in the targeted region and the distance from the epidural electrodes. In particular, might concomitant activation of sensory input come at the price of an increased risk of developing conditions such as neuropathic pain? This was not observed in this preliminary subcohort in line with preclinical findings that endogenous undirected compensatory plasticity might even be reduced (Courtine et al., 2009). Are there also stimulatory effects on inhibitory pathways (Ib inhibitory interneurons)? Do the weak muscle forces observed after application of low voltage (0.5–1.5 V)—weaker than those seen in the absence of stimulation—reflect the activation of inhibitory interneurons? Of note, even though clonus in smaller muscles was reported during stimulation, voluntary movements by larger muscles were not affected by spasticity.

Besides putative side effects, additional beneficial aspects of epidural stimulation might also be unravelled in further studies. For example, can epidural stimulation at L1-S5 ameliorate supraspinal bladder control? The stimulated region includes the innervation area of the inferior mesenteric ganglion (Th12-L2), which transmits sympathetic signals to the hypogastric nerve to innervate the detrusor muscle of the bladder, and the internal bladder sphincter. In analogy to volitional leg movements, regained integration of supraspinal bladder control could conceivably ameliorate voluntary control of micturition. An effect on somatic innervation via the pudendal nerve (S3) might also be possible, and testable via somatosensory evoked potentials. Finally, given the increased innervation of intercostal muscles, improved ventilation of the lungs might reduce the susceptibility of immune-suppressed spinal cord injury patients to pneumonia (Riegger et al., 2009).

Apart from the identification of additional secondary endpoints, upcoming challenges are those inherent to early stage clinical trials, in particular whether the findings can be extended to a broader patient group. As this cohort represents a select subgroup within a larger ongoing study, it remains to be established whether ‘non-discomplete’ patients who lack residual ‘silent’ anatomical connections will respond to epidural stimulation in a similar manner. In principle, this may indeed be possible, since the late-responder in this study is likely to be a ‘non-discomplete’ patient. Moreover, de novo plasticity of the corticospinal fibres tracts sprouting on propriospinal neurons has been shown to contribute to spinal connectivity after spinal cord injury (Courtine et al., 2008). Full weight-bearing movements were observed even after loss of all descending supraspinal long-tract axons (Courtine et al., 2008, 2009) most likely because of the formation of propriospinal relay connections (Courtine et al., 2008). The question of extending findings also pertains to patients taking anti-spasticity medication. Such patients were excluded from the current study, but the majority of patients (40–78%) will develop spasticity after spinal cord injury (Harrington et al., 2011). In particular, it will be of interest to determine whether an anti-spasticity medication such as the central GABA_B receptor agonist baclofen would interfere with the effect of epidural stimulation. Anti-cholinergic drugs, which are frequently used to treat neurogenic bladder dysfunction, might also shift the neurotransmitter balance at the stimulation site, and these potential interactions require clarification. Relating the current findings to measures of daily activity (Scivoletto et al., 2013) and inclusion of appropriate controls will represent important next steps.

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**References**


Predictors of early-onset cognitive impairment

Dementia is a major global health crisis with an estimated 35 million people diagnosed at present, and that number is projected to triple by 2050. Many more suffer from mild cognitive impairment (MCI), which is recognized as a precursor for many types of dementia (Petersen et al., 2014). At the recent G8 Summit in London, health ministers from participating countries discussed dementia and its treatment and prevention (Fox and Petersen, 2013), and issued a communiqué calling for increased research into the mechanisms of disease, and increased efforts targeted at prevention (G8 Summit, 2013). To that end, the identification of lifestyle factors that may contribute to the development of dementia is crucial. In the current issue of Brain, Nyberg and colleagues present data from a longitudinal study in which they reveal the contribution of two such factors—early cardiovascular fitness and cognitive fitness—to the risk of early-onset dementia and MCI (Nyberg et al., 2014).

Longitudinal studies such as these are much needed. In 2010, an NIH ‘State of the Science’ report concluded that there was insufficient evidence to support the use of pharmaceutical agents, dietary supplements or other means for the prevention of cognitive decline or Alzheimer’s disease (NIH State-of-the-Science, 2010). Having reviewed the literature, attendees at the conference concluded that the appropriate longitudinal studies had not been conducted to validate any interventions. Of note, studies that have investigated modifiable lifestyle risk factors for MCI or dementia have typically assessed risk factors in midlife at best, or more often than not, in late life. The relatively few studies that have assessed risk factors acquired before early adulthood have focused on risk of late-onset dementia as their endpoint. For example, the Aberdeen 1921 and 1936 Birth Cohort Studies have access to obstetric and neonatal records of 667 hospital births in 1921, and to the Scottish Mental Surveys of childhood mental ability test scores for children born in 1921 and in 1936, providing a wealth of information with which to examine early life risk factors for later life cognitive impairment (Whalley et al., 2011). However, these cohorts were not representative of the United Kingdom. Furthermore, the relatively small subsets that were successfully traced and alive and eligible for research were studied from the ages of 77 to 88 years and from 64 to 68 years, respectively, precluding investigation of the contribution of neonatal factors, childhood intelligence, and early-life cognitive abilities to the risk of early-onset dementia.

Early-onset dementia is an understudied condition, with the exception of the rare autosomal dominant mutations that produce early-onset Alzheimer’s disease. However, such cases constitute only a small fraction of all cases of early-onset dementia. Nyberg and colleagues now report the results of a study into the impact of cardiovascular fitness and cognitive performance at age 18 in over 1.1 million Swedish male conscripts examined between 1968 and 2005 (Nyberg et al., 2014). The men were followed for up to 42 years, and performance at the time of enrolment was correlated with the risk of developing MCI and dementia later in life. The study focused on early-onset (before the age of 65 years) of dementia and MCI as endpoints and controlled for many confounding factors.

Nyberg and colleagues (2014) exploited this unique data set to evaluate lifestyle predictors of cognitive decline. They concluded that a combination of low cardiovascular fitness and poor cognitive performance in early adulthood was associated with a nearly 14-fold increase in the risk of early-onset MCI and an 8-fold increased risk of early-onset dementia. Low cardiovascular fitness and poor cognitive performance were also independently associated with increased risk of dementia.

References


