LETTER TO THE EDITOR

Harnessing neuroplasticity for clinical applications

Jonathan R. Wolpaw

Laboratory of Neural Injury and Repair, New York State Department of Health and State University of New York, NY 12201-0509, USA

Correspondence to: Jonathan R. Wolpaw, Laboratory of Neural Injury and Repair, Wadsworth Centre, New York State Department of Health and State University of New York, Albany, NY 12201-0509, USA
E-mail: wolpaw@wadsworth.org

Sir, The recent review article ‘Harnessing neuroplasticity for clinical applications’ (Cramer et al., 2011) is in many respects an impressively sophisticated summary of current knowledge of CNS plasticity and its potential translation to important new therapeutic applications. However, this otherwise excellent article has one very major omission: anyone reading it who did not already know better would assume that neuroplasticity essentially ends at the foramen magnum. Apart from several brief references to corticospinal tract plasticity, there is no mention of spinal cord plasticity, of its importance in sensorimotor function, and of the rapidly growing evidence that appropriate engagement and guidance of spinal cord plasticity could play a major role in restoring useful function after spinal cord injuries, strokes and other trauma or disease. A major area of active and successful research that applies directly to the subject of the article, ‘Harnessing neuroplasticity for clinical applications,’ is not addressed.

A full review of activity-dependent spinal cord plasticity and its potential clinical applications would be nearly as lengthy as Cramer et al. (2011). The relevant information comprises at least six substantial bodies of data, three coming from pathological situations or reduced preparations and three coming from normal life. These six areas are briefly summarized and illustrated here.

First, the long-term changes in spinal cord function that develop after injury or disease disrupt supraspinal control have been recognized for at least a century (Riddoch, 1917; Brodal, 1981; Hiersemenzel et al., 2000; Wolpaw and Tennissen, 2001). Indeed, long-term survival after spinal cord injury depends on meticulous bladder, bowel and skin-care regimens that serve to moderate this plasticity. Perhaps, the best early laboratory evidence of activity-dependent spinal cord plasticity was Anna DiGiorgio’s (1929, 1942) demonstration that a short period of abnormal descending activity produced by a hemicerebellar lesion causes a lasting change in spinal cord function. Figure 1A illustrates this striking phenomenon.

Secondly, laboratory studies over the past 60 years have demonstrated that the isolated adult mammalian spinal cord has a remarkable capacity for activity-dependent plasticity. Shurrager and Dykman (1951) showed in cats with complete spinal cord transections that the isolated spinal cord could learn to walk better with training. Over the past 30 years, this work has been greatly extended: anatomical and physiological mechanisms are being defined; and potential clinical applications are being explored (Courtine et al., 2009; Edgerton and Roy, 2009; Rossignol and Frigon, 2011; Rossignol et al., 2011) (Fig. 1B). Over the same period, other studies have described both classical and operant conditioning in the isolated spinal cord (Durkovic and Damianopoulos, 1986; Grau et al., 2006).

Thirdly, much of the excitement now surrounding the possibilities for restoring function after spinal cord injury concerns methods for inducing, facilitating and guiding spinal cord plasticity. These include methods: (i) to reduce scarring and facilitate axon regrowth; (ii) to replace lost neurons and preserve those that remain; (iii) to encourage other adaptive responses to injury; and (iv) to re-establish functionally effective synaptic connections (Fouad et al., 2011; Marsh et al., 2011). These methods seek to enable, augment and guide the spinal cord’s intrinsic capacities for plasticity (e.g. Fig. 1C).

Fourthly, both human and animal studies show that the acquisition of basic behaviours such as locomotion and withdrawal from pain depends on perinatal spinal cord plasticity, which is guided by the brain and sensory input (Myklebust et al., 1982, 1986; Eyre et al., 2001; Martin et al., 2004; Schouenborg, 2008).
Figure 1  Six representative examples of activity-dependent spinal cord plasticity. The first three (A–C) illustrate spinal cord plasticity in pathological situations or in reduced preparations. The next three (D–F) illustrate spinal cord plasticity in normal life. (A) A hindlimb postural asymmetry produced by a unilateral cerebellar lesion persists after complete transection of the thoracic spinal cord. The cerebellar lesion occurred 60 min prior to the spinal cord transection. Scale bar = 2 cm. Modified from Chamberlain et al. (1963). (B) Impact of a combined treatment of serotonergic agonists, epidural electrical stimulation and locomotor training on treadmill locomotion (i.e. at 4 cm/s) in spinal-transected rats. Data from an untreated and a treated rat are shown on the left and right, respectively. Top: a stick diagram
The absence or distortion of these essential early influences (e.g. due to cerebral palsy) produces an abnormal adult spinal cord and associated motor deficits (e.g. Fig. 1D). In such situations, methods for ensuring more normal spinal cord plasticity early in life might substantially improve adult motor function (e.g. Carmel et al., 2010).

Fifthly, human and animal studies show that the acquisition of motor skills in adult life is associated with changes in spinal reflex pathways (Wolpaw, 2010). For example, professional ballet dancers have unusually small stretch reflexes and H-reflexes in their leg muscles (Fig. 1E) (Nielsen et al., 1993). This reflex depression probably contributes to their ability to maintain the muscle co-activations important in this form of dance, and thus appears to constitute a significant part of the CNS plasticity that underlies the acquisition of this complex athletic skill. Spinal proprioceptive reflexes change also with ageing and during the acquisition of more limited skills such as backward walking (Meyer-Lohmann et al., 1986; Koceja et al., 1995; Schneider and Capaday, 2003; Dragert and Zehr, 2011). Similarly, the success of rehabilitation regimens in restoring function after stroke or in other disorders is likely to depend significantly on the plasticity they induce in spinal reflex pathways.

Sixthly, humans, monkeys, rats and mice can change spinal reflex pathways when rewarded for doing so (Wolpaw, 2010). These changes occur gradually over days and weeks of exposure to an operant conditioning protocol. The conditioning protocol creates a hierarchy of plasticity in which plasticity in the brain, acting through the corticospinal tract, induces the plasticity in the spinal cord that underlies the larger (or smaller) reflex. This spinal cord plasticity includes changes in motor neuron synaptic inputs (e.g. Fig. 1F) and intrinsic properties (e.g. firing threshold and axonal conduction velocity (Carp and Wolpaw, 1994; Carp et al., 2001)); and it affects other behaviours, such as locomotion. Thus, appropriate reflex conditioning can improve locomotion after spinal cord injuries (Chen et al., 2006). Conditioning protocols that target selected spinal pathways (e.g. selected on the basis of the individual’s specific functional deficit) are a promising new approach to restoring useful function after spinal cord injury or other trauma or disease.

In addition to these six distinctive bodies of data, two further considerations indicate the importance of spinal cord plasticity to the development of effective new rehabilitation therapies. First, because the spinal cords and the analogous brainstem nuclei are the final common pathway for all behaviours, the many forms of brain plasticity described in Cramer et al. (2011) can have no functional effect whatsoever unless and until they alter the activity of spinal cord motor neurons. Thus, the functional impact of brain plasticity necessarily depends on its interactions with spinal cord plasticity. As a result, increased understanding and engagement of spinal as well as supraspinal plasticity is essential for the realization of effective new therapies.

Secondly, the spinal cord has major advantages over other CNS areas as a venue for identifying and understanding the many kinds of plasticity that might be induced and guided so as to improve function. The spinal cord is relatively simple and accessible, its major cell types and pathways are well known, and its connections with the periphery and the brain are accessible to monitoring, to direct excitation and to short-term or long-term interruption. Furthermore, because the spinal cord connects directly to behaviour, the problem of defining the functional impact of plasticity is easier than it is for other CNS regions. These unique advantages (which have made the spinal cord a remarkably productive experimental model for at least 150 years) make the spinal cord a logical place to define mechanisms and principles of plasticity that are likely to apply throughout the CNS, and to develop the clinical applications of this plasticity.

In sum, spinal cord plasticity occurs throughout life in both health and disease, combines with brain plasticity to change behaviour in complex ways and offers numerous possible avenues for inducing functional recovery beyond that possible with current

**Figure 1 Continued**

decomposition of hindlimb motion during swing. Also shown are limb end-point trajectories (with red indicating the initial drag phase of swing) and vectors representing the direction and magnitude of limb end-point velocity at swing onset. The rat’s per cent of body weight support (BWS) is indicated. Bottom: sequences of EMG activity from tibialis anterior (TA) and soleus (Sol) muscles. Grey and red bars indicate the stance and drag phases, respectively. Locomotion is far more normal, effective and consistent in the treated rat. Modified from Courtine et al. (2009). (C) Reconstruction of a propriospinal commissural interneuron in the rat spinal cord that has regenerated through a midline lesion made 72 days earlier and formed collaterals. The arrowhead indicates the soma of this neuron. The regenerated axons of such neurons make functional synapses. The arrow marks the place where the regenerating axon bifurcated and continued rostrally and caudally (branches not shown for clarity). Also shown is another neuron that has not regenerated across the lesion and terminates in a growth cone (asterisk). Scale bar = 200 μm. From Fenrich and Rose (2009). (D) The direction of flexion withdrawal responses to painful stimuli in normal adult rats and in adult rats in which the spinal cord was transected just after birth. In normal adults, the direction of the response is almost always correct (i.e. the limb moves away from the painful stimulus), while in transected adults it is often incorrect (i.e. the limb moves towards the stimulus). Neonatal spinal cord transection abolishes the descending input that gradually shapes normal (i.e. correct) flexion withdrawal responses. Modified from Levinsson et al. (1999). (E) Soleus H-reflexes are much smaller in professional ballet dancers than in other well-trained athletes (e.g. runners, swimmers and cyclists). (H-reflexes of sedentary subjects fall in between.) The dancers’ smaller reflexes appear to be an important component of skill acquisition. Modified from Nielsen et al. (1993). (F) Soleus motor neurons (dotted lines) from a control rat (top) and a rat in which the soleus H-reflex was reduced by an operant down-conditioning protocol (bottom). Arrows point to GABAergic terminals on the somatic membrane. The terminals are identified by glutamic acid decarboxylase (GAD67)-immunoreactivity. After down-conditioning, soleus motor neurons have many more GABAergic terminals, and these terminals are more densely labelled and cover more of the somatic membrane. The increase in GABAergic terminals is likely to be a component of the spinal cord plasticity that produces the smaller H-reflex. Scale bar = 20 μm. See Wang et al. (2006) for full information.
therapies. By briefly summarizing the current state of knowledge in this area, this letter hopefully fills a major gap in the otherwise excellent review of Cramer et al. (2011).

Acknowledgements

Drs Jonathan S. Carp, Xiang Yang Chen and Elizabeth Winter Wolpaw provided valuable comments on the manuscript.

Funding


References


DiGiorgio AM. Influences of the cerebellum-neocerebellum on the postural tone of the limbs and cerebellar somatotopy in the rhomboencephalic animal. Arch Fisio 1942; 42: 25–79.


Riddoch G. The reflex functions of the completely divided spinal cord in man compared with those associated with less severe lesions. Brain 1917; 40: 264–402.


Wolpaw JR. What can the spinal cord teach us about learning and memory? Neuroscientist 2010; 16: 532–49.