Experimental spinal cord injury is no longer incurable. Many papers have appeared over the past few years reporting functional recovery following a variety of treatments. These have included interventions that affect myelin inhibitory molecules and their receptors, or inhibitory chondroitin sulphate proteoglycans, and treatments in which the regenerative potential of axons has been stimulated through growth-factor receptors or manipulation of internal signalling pathways (for reviews see Buchli and Schwab, 2005; Fawcett, 2006; Hannila et al., 2007). There has also been success with strategies that bridge the injury using various axon growth-promoting cell types (Fouad et al., 2005; Biemaskie et al., 2007; Raisman and Li, 2007). Functional recovery has been seen in hindlimbs and forelimbs and affecting walking, skilled movements, sensation and other outcome measures. This is all very encouraging, but it is still not entirely clear what changes are responsible for the recovery. Many of the successful treatments stimulate axon regeneration through the site of injury, but most also stimulate plasticity. In the field, plasticity is used as a term to describe short-distance sprouting above and below the lesion and changes in synaptic strength, together enabling the CNS to change its connectivity. Thus, treatments that affect NogoA signalling and chondroitin sulphate proteoglycans, in addition to stimulating spinal cord axon regeneration, also promote reactivation of ocular dominance, the most studied example of plasticity (Pizzorusso et al., 2002; McGee et al., 2005). Is functional return in the injured cord due to the small number of axons that regenerate, or due to plasticity in the remaining uninjured axons? The only definitive way to sort this out in paradigms of injury that do not completely cut the cord (as in most experiments), is to re-lesion the regenerated axons. However, this causes a new spinal injury that kills many previously uninjured axons. In only one case has it been possible to re-lesion without the confusion of collateral damage. In this experiment, axons were bridged across a lesion by a peripheral nerve graft with chondroitinase applied at either end to digest inhibitory chondroitin sulphate proteoglycans, leading to recovery of forelimb function. The only other way to be sure that regenerated axons have brought back function is to study complete transactions, and use as an outcome measure a behaviour that requires conduction through the lesion, for instance co-ordination of hindlimb and forelimb stepping (Fouad et al., 2005). Another definitive way in which regenerated axons can be shown to restore function is to study the effects of sensory fibres that have grown back into the cord after complete dorsal root section or avulsion. A recent study published in this issue of Brain shows this particularly elegantly (Ibrahim et al., 2009). Sensory axons attempting to regenerate back into the spinal cord usually get stuck at the scar-like interface between PNS Schwann cells and CNS astrocytes at the dorsal root entry zone. However, there is a population of axons that have to be able to penetrate astrocytes and grow in the CNS throughout life. Olfactory axons from olfactory receptors are born continuously and are ushered through the astrocytic barrier on the outside of the CNS by olfactory ensheathing glia. Ibrahim and colleagues implanted olfactory glia into the gap between avulsed dorsal roots and the dorsal root entry zone, with the remarkable effect that the olfactory glia interleaved with the dorsal root entry zone astrocytes, decreasing their scarring reaction and making a pathway over which sensory axons were able to regenerate back into the cord. That the axons were able to make functional connections was shown electrophysiologically and through the animal’s recovered ability in skilled paw function.

Despite these definitive proofs that regenerated axons in the damaged spinal cord can restore function, it is probable that much of the useful recovery seen following treatment of animals with partial spinal cord lesions is due to the stimulation of plasticity. A simple indicator of this is that functional recovery in many experiments is seen as soon as 1 week after injury—too fast for axons to have regenerated and formed connections (Bradbury et al., 2002). The laboratory of Martin Schwab has been particularly active in demonstrating that there can be extensive sprouting in the injured spinal cord, which can be enhanced by treatment with anti NogoA (Bareyre et al., 2004; Freund et al., 2006). The corticospinal tract and rubrospinal tracts, interneurons, sensory, serotonergic and adrenergic axons have all been shown to make
new local sprouts after injury. Some of these new sprouted connections are clearly anatomically abnormal; for instance when one corticospinal tract is lesioned the contralateral tract can sprout across to the denervated side of the cord (Barritt et al., 2006). Yet these events are associated with functional improvements. In a recent paper published in Brain, Maier et al. (2009) advanced the concept of treatment-induced plasticity, performing a very detailed analysis of stepping behaviour following partial spinal cord injury, and examining the effect of blocking NogoA. As in previous work, the treatment increased axon regeneration and sprouting, and it also allowed the animals to regain a more normal stepping behaviour. The investigation then took a further innovative step by asking whether combining anti NogoA with a rehabilitation regimen might further improve function. The rationale for this idea comes from studies of development. Here, there is an initial period of exuberant connections, which are subsequently refined down through an activity and behaviour-driven mechanism. Treatment with regeneration and plasticity-inducing treatments such as anti NogoA might be thought to produce a similar exuberance of random connections that would then benefit from a behaviourally driven refinement leading to improved function. The reality of the experiment was somewhat different: some groups of animals in the experiment were given daily locomotor training on a treadmill—20 min for the hindlimbs and 20 min for all four limbs. Animals that received daily training alone showed improvement in their stepping ability and in its consistency. The surprise came from the animals that received both anti NogoA and daily rehabilitation. These animals developed a very abnormal stepping performance, with great variability from step to step, all of which made their ability to step and to climb a slope worse. One possible explanation was that the animals were experiencing pain on walking, but this was investigated and discounted. The most likely explanation is that animals ‘self-train’ as they move around their boxes, and in the presence of enhanced plasticity due to anti NogoA the result is a beneficial selection of the new connections that are enabled by the antibody treatment, leading to better functional recovery. However, the daily treadmill training was teaching the animals a very different stepping and walking strategy, so the ‘self-training’ and rehabilitation training had conflicting effects on spinal cord circuitry. Other experiments have shown that training in one context can have negative effects on animals’ abilities in a different behaviour (Bigbee et al., 2007; Girgis et al., 2007).

The results of Maier et al. (2009), Girgis (2007) and Bigbee (2007) have important implications for rehabilitation treatment in neurological disorders. First, behaviours can compete, and training in one behaviour can have negative consequences for another. It is clearly important that a rehabilitation task does not compete against a behaviour that patients are performing naturally. Second, making the CNS plastic with treatments such as anti NogoA can enhance the effects of rehabilitation, in both positive and negative directions. The nervous system rendered plastic by treatment is vulnerable, and while it has a greater capacity to respond positively to rehabilitation, it also has a greater capacity to respond negatively to a suboptimal rehabilitation strategy.

James W. Fawcett
Department of Clinical Neurosciences,
Cambridge University Centre for Brain Repair,
Cambridge CB2 0PY, UK
E-mail: jf108@cam.ac.uk
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