

initially random formation of putative synapses followed by the retraction of all filopodia that failed to make contact—thus, synapses appear to stabilize dendrites.

The study by Niell *et al.*¹ is perhaps the first to actually watch potential synapse loss during synaptogenesis in the CNS. As in cultured neurons⁹, the authors found that synapse disassembly, suggested by a significant decrease in PSD-95-GFP puncta fluorescence, seemed to take place before dendrites retracted. Why would synapse disassembly cause dendritic terminals to retract? One possibility is that resources needed to maintain or extend new dendrites may be limited; therefore, retraction in regions with undesired inputs would facilitate dendritic extensions elsewhere. Reiterations of this process would tend to bias dendritic elaboration and growth toward regions containing appropriate presynaptic

terminals. The current live-imaging study thus supports this ‘synaptotropic model’ put forth a number of years ago based on electron microscopy observations¹². This model might explain, in part, how asymmetrically organized dendritic arbors are established in some sensory systems such as the retina and barrel cortex where preferred afferents are organized into specific subregions of the tissue^{2,14}. Further live-imaging studies of dendritic behavior and synapse development, in circuits where one can distinguish between appropriate and inappropriate presynaptic terminals, should provide a deeper insight into how some connections are maintained and others eliminated. Given that zebrafish are an excellent model for studying circuit development *in vivo*, such imaging studies using this model system will undoubtedly be fruitful.

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Just one word: plasticity

Andrew R Blight

A new study shows that after injury of the corticospinal tract in the rat spinal cord, spontaneous recovery of function involves extensive plastic changes in the connectivity of multiple types of neurons distributed throughout the central nervous system.

The ability of the adult mammalian central nervous system (CNS) to recover from injury is sometimes remarkable and at other times frustratingly limited, but in either case it remains poorly understood. Nowhere has the frustration and lack of understanding been greater than in the case of the injured spinal cord, where limitations on recovery seem particularly severe. Plasticity of connections in the spinal cord provides some capacity for adaptation to injury^{1,2} and represents a target for therapeutic manipulation^{3,4}. When one pathway from the brain to the motor systems of the spinal cord is interrupted, another parallel pathway can take over the role of the missing projection, by a process of collateral sprouting. In this issue, Bareyre *et al.*⁵ demonstrate a surprisingly extensive capacity for spontaneous functional reorganization in spinal circuits. This plasticity does not occur at one level of the neural network, but crosses over to parallel pathways and extends to both upstream and downstream components.

These new data present an encouraging vision of what might be possible with additional therapeutic intervention. They should also stimulate us to reevaluate some of the existing literature in the field of spinal cord injury with a new appreciation for the potential complexity of functional reorganization.

In their study⁵, Bareyre *et al.* revisit a familiar experimental model: dorsal hemisection of the lower thoracic spinal cord in rats. Their laboratory and many others have used this model, in which the upper half of the spinal cord is surgically transected, to examine interventions that might stimulate regeneration of central axons in the dorsal corticospinal tract (CST), which is completely severed by the injury. Under normal circumstances, the CST does not regenerate through or around the hemisection lesion. However, it does show modest sprouting of collaterals into the gray matter from surviving axons proximal to the injury. Dorsal hemisection produces functional deficits in the hindlimbs, particularly a loss of tactile placing responses, which partially recover over several weeks. The possibility that proximal sprouting of the CST might contribute to this recovery has generally seemed unlikely, given the complexity implicit in

substituting an indirect pathway for the normal direct innervation of lumbar motor centers. This would seem to require an unexpected degree of goal-directed reorganization.

A more likely substrate for recovery of function is provided by compensatory sprouting of the ventral CST, which contributes to the recovery of forelimb function¹ after a similar transection of the dorsal CST in the cervical spinal cord. It is relatively simple to visualize how this kind of sprouting might be organized, based on a commonality of targets for the damaged and sprouting parts of the same corticospinal system (Fig. 1). This ability of partially damaged systems to compensate may represent a beneficial extension of normal processes of synaptic turnover and maintenance in adult CNS, though it seems limited to injuries in which there is some surviving component of the damaged projection that can be expanded.

Bareyre *et al.* found, however, that the number of collaterals from hindlimb motor cortex neurons to the cervical spinal gray matter increased fourfold in the 3 weeks after thoracic CST transection (Fig. 1). About half of this initial increase was lost by 12 weeks, but the authors were able to show that most of the

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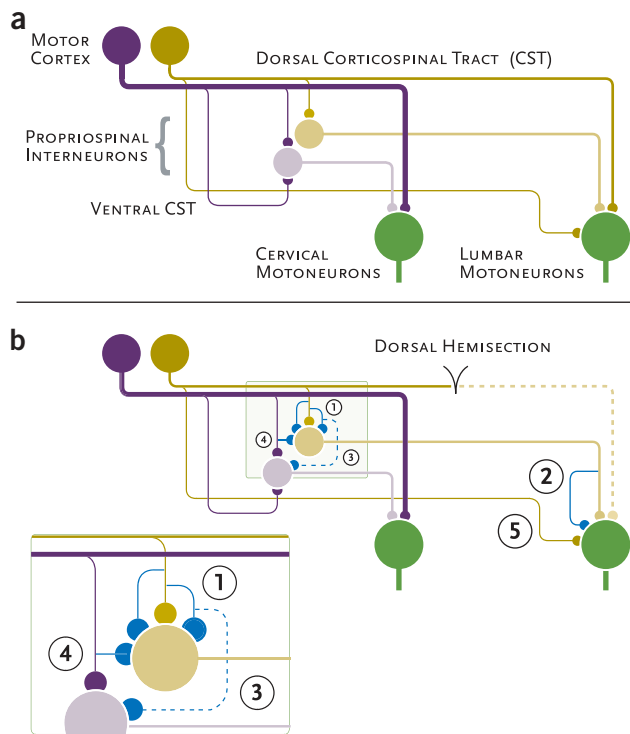


Figure 1 Observations of Bareyre *et al.* (a) The rat corticospinal motor system, including pyramidal cells in the motor cortex, lumbar motoneurons and cervical propriospinal interneurons, which project either to cervical or lumbar motor pools. The precise nature of neuronal projections, including the branching site of new collaterals and the degree to which synapses are formed directly on motoneurons¹² is not entirely clear and much more complex than illustrated here. (b) After dorsal hemisection of the lower thoracic spinal cord, involving complete transection of the dorsal corticospinal tract, increased synaptic projection (blue) was seen from hindlimb motor cortex to long propriospinal interneurons projecting to lumbar motor pools (1), from those same propriospinal neurons, within the lumbar motor system (2), at 3 weeks after injury, from hindlimb motor cortex to short propriospinal interneurons within the cervical cord (3, though many of these presumably inappropriate connections appeared to be lost again at 12 weeks); and from forelimb motor cortex to hindlimb motor pool (4), most likely through sprouting at the level of propriospinal neurons in the cervical cord. Pronounced sprouting was not seen from the ventral CST (5), though some sprouting may occur, based on earlier findings with cervical transection of the CST injury¹.

new connections that were lost during this time projected to short propriospinal neurons, whose axons remain within the cervical spinal cord. Connections to long propriospinal neurons, projecting to the motor pools of the lumbar cord, apparently the most useful, were retained. The investigators were then able to show that the long propriospinal axons themselves increased their projections in the lumbar motor pool. To provide additional evidence that a new intraspinal pathway had been formed by this combination of first- and second-order sprouting, they did transynaptic retrograde tracing by injecting pseudorabies virus into the hindlimb muscles. They saw a 4–5 fold increase in the labeling of pyramidal cells in the motor cortex with virus injected at 3 or 12 weeks after dorsal hemisection, in addition to the expected labeling of long propriospinal interneurons in the cervical spinal cord.

Partial functional recovery of the hindlimb placing responses developed gradually over the weeks after the CST lesion, consistent with a functional benefit of the increased cortico-spinal connection. Unilateral transection of the pyramidal tract in the brainstem produced a significant loss of that recovery on the affected side, indicating that the recovery of placing was dependent on new projections of the CST. The increased projection from cortex to lumbar motor systems was also confirmed electrophysiologically. Microstimulation of the cortex produced hindlimb muscle activation in uninjured animals and, at slightly higher threshold and latency, in animals at 12 weeks after injury, but not in animals after only 3 days or 3 weeks of recovery. Again, this electrophysiological recovery could be abolished by a second, unilateral transection of the CST in the brainstem.

One additional finding emerged from the studies. Retrograde labeling with pseudorabies virus from the periphery revealed an ‘upstream’ reorganization of corticospinal connections. Approximately a quarter of the labeled neurons in the cortex of animals recovering from the dorsal CST lesion were outside the normal hindlimb area; most were found in the forelimb area of the cortex, but a few came from outside the motor representation altogether. Therefore, the processes of reorganization started by the dorsal hemisection spread well beyond the neurons that were directly damaged, including other pathways within the local spinal cord, the target motor systems in the lumbar cord, and related populations of cells in the motor cortex of the brain.

Changes in connectivity are likely to be even more widespread than the Bareyre *et al.* study has revealed. Compensatory sprouting of the ventral CST has already been detected in cervical cord, and is likely to occur in this model too, though it was not possible to resolve such changes here, perhaps because of the modest contribution of the ventral CST to the hindlimb motor system. There are also likely to be changes in other ascending and descending projections that were not examined, but which are damaged by the hemisection lesion². Some of these may contribute to the overall functional recovery that is seen. This, however, does not diminish the remarkable extent and apparent functionality of the changes that were measured.

The human CNS may be very different in its responses to injury, as compared to the rat. Nonetheless, there is evidence of widespread reorganization of connections in human CNS derived from studies in people with spinal cord injury. Precise interpretation of these changes is difficult, given the complexity and severity of spinal lesions in such cases^{6–8}.

The signaling process responsible for these widespread changes is not at all clear. Still more obscure is the mechanism that allows newly formed connections to be retained or lost, based on their overall usefulness, as seems to be the case with the new connections to the short propriospinal interneurons. If a feedback mechanism exists to signal whether a neural connection is ‘right’ or ‘wrong’, it seems to require integration at the very highest level. Intuitively, such a mechanism seems to be in action under conditions, such as amateur athletics, that test the performance of our sensorimotor systems. This is expressed with characteristic remorse by the poet Philip Larkin⁹ as he describes tossing an apple core at a waste basket:

*Watching the shield core
Striking the basket, skidding across the floor,
Shows less and less of luck, and more and more
Of failure, spreading back up the arm...*

Over the last century, research on improving recovery from spinal cord injury has concentrated on ‘regeneration’—the concept of recapitulating developmental growth of long axons in the nervous system. Relatively little attention has been directed to the processes of plasticity by which the nervous system fine-tunes structure and function to meet the demands of the body in its environment. This is at least in part because they involve smaller-scale, shorter collateral growth and synaptic changes that are much harder to visualize and quantify. Indeed, Bareyre *et al.* have achieved something of a technical *tour de force* by combining multiple types of anterograde and retrograde staining with the available functional measures.

In the most severe types of spinal injury, involving complete transection, it seems that

plasticity of existing connections would have relatively little to offer, without first regenerating some connection across the gap between brain and distal spinal cord. However, most spinal injuries are neurologically incomplete and therefore susceptible to improvements in residual connections. Similarly, it is likely that any success that we have in regeneration will also be incomplete. Therefore, plasticity is likely to be an important adjunct therapy, even if we are eventually successful in stimulating partial regeneration of the type seen in lower vertebrate spinal cord. Growth inhibitors such as Nogo and the chondroitin sulphate proteoglycans in the central nervous system, initially of interest for their potential impact on regeneration, have shown increasing evidence of parallel inhibition of spontaneous plasticity^{3,10,11}. We may find that enhanced plasticity rather than regeneration is the main justification for developing blockers of growth inhibition as therapeutic agents for CNS injury.

Bareyre *et al.* have expanded our appreciation of the capacity for meaningful reorgani-

zation of spinal cord circuitry. Their work should help to reinvigorate interest in this area, and if one were obliged to offer dinner-party advice to a current graduate in neuroscience, it would be reasonable to point to this important, fascinating and slightly mysterious area with just one word: plasticity.

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Understanding awareness: one step closer

Steven J Luck

Attention enhances neural and behavioral responses to visual objects, but how does this affect our conscious perception? Attending to an object increases our subjective experience of stimulus contrast, reports a study in this issue.

How does the biophysical machinery of the brain evoke our rich phenomenological experience of the world? This question was once thought to be beyond the range of scientific inquiry, but leading neuroscientists have begun to find interesting answers by studying the neural correlates of awareness^{1,2}. Most of these experiments examine how brain activity differs when an observer reports being aware versus unaware of a given sensory input. However, these studies ignore the quality of our phenomenological experience (for example, the difference between what it’s like to see blue and what it’s like to see red). This approach to awareness is a bit like an art critic classifying Van Gogh’s *Starry Night* as “a dark picture” and Monet’s *Garden at Giverny* as “a light picture,” ignoring the dimensions of color, technique, composition and expression.

In this issue, Carrasco and colleagues³ provide a step toward a richer and yet still rigorous description of awareness. This study addresses phenomenological experience in the context of a very old question about perception: does paying attention to an object change its appearance? Attention is often likened to a spotlight⁴ or zoom lens⁵ that brightens or sharpens our perception, but no one has convincingly shown that attention actually changes our phenomenological experience of the world. Many studies have shown that attending to an object amplifies and sharpens neural representations of the object^{6–8}, leading to an improved ability to detect the object and report its properties^{9,10}. However, these studies do not show that we actually experience attended objects differently from unattended objects.

The ever-present problem in studies of awareness is that observers’ reports of their experience are very easily biased by a variety of cognitive and affective factors. If observers report that an attended object seems brighter than an ignored object, it is usually impossi-

ble to know whether they really experienced it as being visually brighter. It is always possible that attention did not influence their perceptual experience, but rather that preconceptions about attention led them—intentionally or unintentionally—to report it as being brighter. Carrasco and colleagues have developed a new procedure for assessing an observer’s experience that markedly reduces the influence of bias on such reports.

In this procedure (Fig. 1), observers were shown two oriented gratings and asked to report the orientation of the higher-contrast grating (the one with brighter brights and darker darks). Thus, the observers explicitly reported the orientation of a grating, and their decision about which grating was higher in contrast was implicit rather than explicit. Attention was manipulated by preceding one of the two gratings with a small dot that automatically attracted attention.

When the two gratings differed greatly in contrast, the attention-capturing dot had no effect: observers simply reported the orientation of the higher-contrast grating. When the

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