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Brain-dependent movements and cerebral-spinal connections: Key targets of cellular and behavioral enrichment in CNS injury models

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Abstract—One of the most difficult problems in experimental and clinical neurology is how to facilitate recovery of the ability to walk voluntarily. Local spinal mechanisms, descending input from the brain, and ascending sensory feedback to the brain are required for non-treadmill, self-initiated stepping. In evaluating the integrity of axons connecting the brain and spinal cord in neural injury models, the selection of behavioral tests may be at least as important as the histological procedures, if not more so. A comprehensive and clinically meaningful test battery should include assessments of brain-dependent movement capacity. Behavioral enrichment procedures that prominently encourage self-initiation of stepping have been used to facilitate plasticity and motor function after brain or spinal cord injury. Progressive degeneration characteristic of parkinsonian models can be slowed or halted altogether by forced exercise and limb use. Behavioral interventions may work partly because the animal adopts alternative behavioral strategies to compensate for impaired performance. However, mounting evidence suggests that motor rehabilitation can also promote restoration of function or prevent slow degeneration of tissue by engaging constitutively available mechanisms that protect, repair, rewire, or reactivate cells.

Key words: exercise, forced-use therapy, motor enrichment, Parkinson's disease, plasticity, neurotrophic factors, spinal cord, stroke, traumatic brain injury.

INTRODUCTION

Among central nervous system (CNS) injury models, one of the most disabling impairments is the inability to initiate weight-shifting steps. In spinal cord injury, as well as in Parkinson's disease and stroke, walking voluntarily is regarded as a major treatment objective of clinical and experimental physiotherapy, neurosurgery, and neurology. Nonvoluntary, assisted treadmill stepping can occur via reactive adjustments in the position of the lower extremities to reestablish the center of gravity. When the leg is moved passively backward by the treadmill, the stepping movement to recover stability can

Abbreviations: BDNF = brain-derived neurotrophic factor, CNS = central nervous system, FGF-2 = fibroblast growth factor 2, GDNF = glial-derived neurotrophic factor, MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, NMDA = N-methyl-D-aspartate, 6-OHDA = 6-hydroxydopamine.

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be essentially reflexive and does not necessarily require higher motor control. In contrast, deliberate weight-shifting steps over ground presumably involve substantial supraspinal participation. For this reason, interventions that might restore or improve connections between the brain and spinal cord are regarded as highly valuable, as are behavioral tests that can evaluate more specifically the integrity of descending pathways associated with the intention to walk.

ASSESSING BRAIN-DEPENDENT MOVEMENT CAPACITY

When using rat models, one must recognize that they are primarily "front-wheel drive" for most functions that involve exploratory spontaneous locomotion. As shown in the **Figure** (and in research movie clips at our web site, www.schallertlab.org), when the forelimbs are lifted off the ground by an experimenter, the rat fails to walk on its isolated hindlimbs. The rat may initiate a step or two with one hindlimb while pivoting on the other, or make a few steps backward or sideways, but voluntary stepping is extremely limited or lacking altogether. In contrast, when the hindlimbs are lifted off the ground, the rat readily initiates stepping movements with its forelimbs, and can walk long distances in this "wheelbarrow" posture [1–5].

When one forelimb is severely impaired by cervical spinal hemisection or severe nigrostriatal dopamine depletion, and the nonimpaired forelimb is lifted off the ground along with the hindlimbs, the rat either fails to step with the impaired forelimb or takes fewer steps that may be smaller in size. When both forelimbs of rats with severe unilateral nigrostriatal injury are on the ground, the impaired limb appears to step, alternating with the nonimpaired forelimb. But the steps the rat takes with the impaired forelimb appear to be catch-up (adjusting) steps

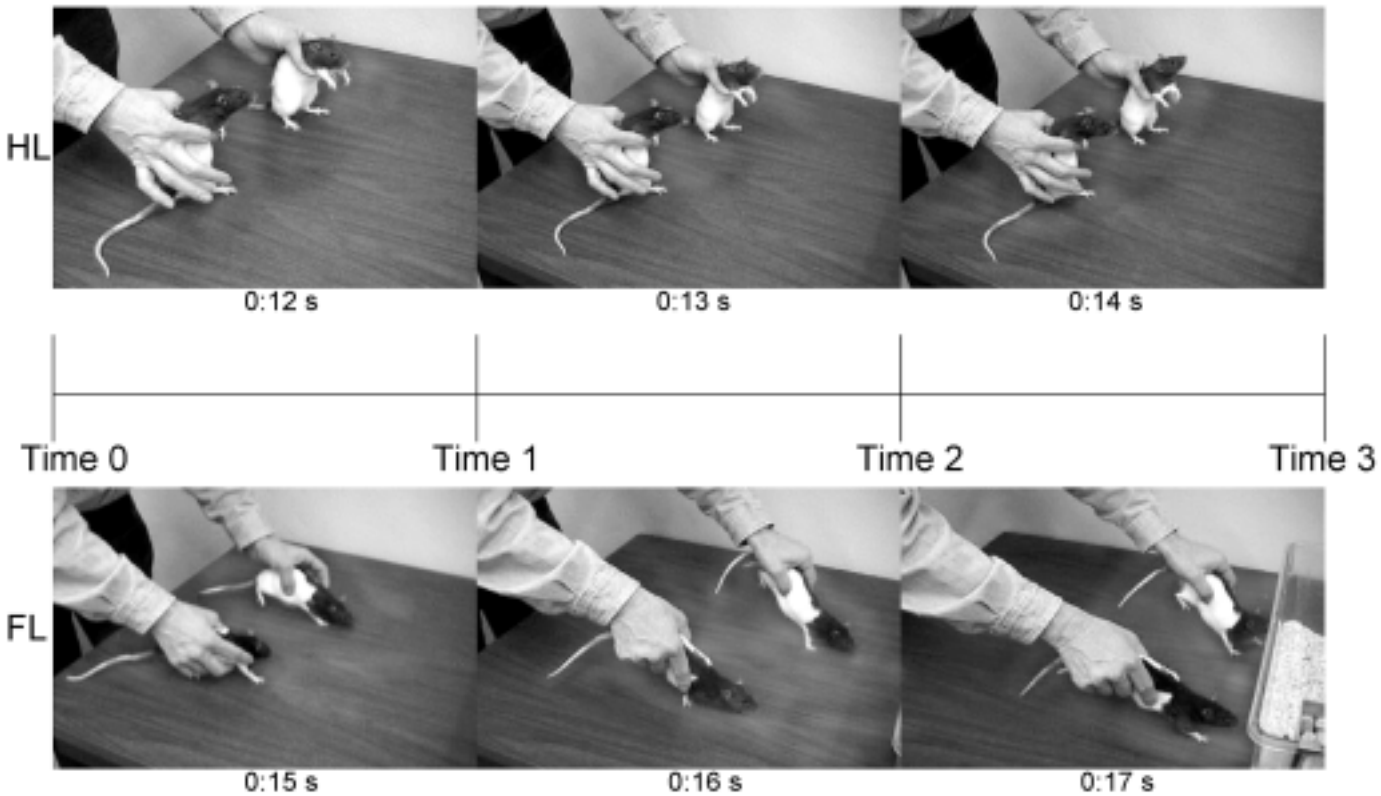

Figure.
"Front-wheel drive": Two rats are placed with either their forelimbs or hindlimbs resting on the ground. Consistent forward stepping is initiated when the forelimbs are on the ground but not when only the hindlimbs are on the ground. Time (s) of selected sequential frames from digital movies is shown. Figure corresponds to full-motion video, "HL Akinetic," available on www.schallertlab.org.

taken in response to the shift in center of gravity caused by the action of the nonimpaired forelimb. In contrast to steps that are initiated spontaneously, catch-up steps do not require an intact dopamine system, although dopamine modulates their speed and size. For this reason, it is difficult to detect impairment in the affected limb unless that limb is examined in isolation [1].

When placed on a moving treadmill, an intact animal can take steps with its hindlimbs that adjust for the shift in center of gravity regardless of whether it is also allowed to use its forelimbs. It is possible, though, that these movements primarily reflect the function of local spinal circuitry with an unknown level of modulation by anterior CNS structures. Moreover, forelimb stepping appears to potentiate hindlimb stepping. After an injury that impairs hindlimb capacity, forelimb behavior may influence recovery and maintenance of hindlimb function.

It should be noted that the hindlimbs do have a well defined role in movement initiation during some behaviors. When a rat swims toward a visible escape platform in a well learned location, the forelimbs are immobile in a forward-pointing posture that provides lift while the hindlimbs paddle [6–9]. Jumping to targets, pushing upward during rearing, and backing out of a tunnel also depend on the hindlimbs to initiate the movement most effectively [10,11]. Models of CNS injury associated with compromised hindlimb function might be improved by examining these behaviors, in part because they may be modulated by inhibitory or excitatory input from the brain.

Since active movement initiation of the forelimbs may be linked to brain control over spinal cord processes, it is important to include behavioral tests that specifically examine this possible link and test each forelimb in isolation. In addition to the isolated forelimb stepping test described above, and a similar test of forelimb weight-shift initiation during rearing and spontaneous lateral exploration of vertical surfaces [2–6], other tests may be useful as well [6,12–17]. One example is the vibrissae-evoked placing test battery. In this series of tests, the rat is held aloft by the experimenter such that neither the forelimbs nor hindlimbs touch any surface. The experimenter brings the vibrissae on one side into contact with the edge of a table (see SchallertLab.org); the sensory input to the vibrissae signals the presence of a stable surface, and the animal immediately places a forelimb onto the table [15,18]. The forelimb not being tested is restrained by the experimenter. Deficits in forelimb placing on this test are present following unilateral cervical spinal injury, nigrostriatal terminal loss, unilateral traumatic brain injury, and focal ischemia. These deficits do not recover after complete cervical spinal cord injury or severe dopamine depletion leading to forelimb akinesia. **Table 1** depicts the forelimb placing deficit in the 6-hydroxydopamine (6-OHDA) hemi-parkinsonian model. Note that the deficit develops over the first week after exposure to the neurotoxin, which suggests that there is a workably long window of opportunity for neuroprotection by behavioral or cellular interventions [19].

Another battery that assesses brain-dependent movement capacity is the adhesive removal test, in which small pieces of sticky tape are placed on the rat's fore- or hind feet, and the animal is timed while it contacts and

Table 1.
Successful placing: Time course of vibrissae-evoked contralateral forelimb placing deficits in rats with severe dopamine depletion caused by 6-OHDA infusion into the nigrostriatal dopamine pathway (medial forebrain bundle, a parkinsonian model). Constraining the nonimpaired forelimb with a cast during days 1–7, the period of ongoing degeneration, forced overuse of the impaired forelimb and spared the ability to place.

Model	Percentage of Successful Placing							
	Pre	Day 2	Day 4	Day 6	Day 8	Day 10	Day 12	Day 14
Sham	100	100	100	100	100	100	100	100
6-OHDA No cast	100	92	25	17	10	15	8	0
6-OHDA Cast, days 1–7	100	92	100	95	100	87	100	92

Note: Data are percentages of successful placing of the affected forelimb onto a table top in response to vibrissae contact with the table edge [4,5].

removes these with its teeth. This likely requires adequate brain-spinal connectedness [12–15,20]. Following thoracic-level spinal damage, one can place the tape on the hind feet and observe the ability of the animal to respond by contacting the tape with the mouth, which should require sensorimotor processes involving both the brain and spinal cord. Simple paw-shaking or a change in the position of the limb during locomotion are two initial reactions to a piece of tape adhered to a paw [12], and may remain even after complete spinal transection [21]. This suggests that, in contrast to the more complex response of contacting the stimulus with the mouth, these simpler behavioral reactions may require little or no modulation by the brain.

In addition to the behavioral tests mentioned above, tests that involve auditory or visual cues that the animal must recognize and respond to specifically with a learned hindlimb movement would require brain control over the spinal cord and might be useful for examining treatments of thoracic-level damage.

Thus, the battery of functional outcome tests used to evaluate the potential clinical benefit of a treatment must be sensitive to the injury acutely and chronically, and also assess exactly the qualitative effects of the treatment on motor or sensory function. This assessment should include whether the treatment might reasonably be expected to improve the brain's command over spinal neurons associated with behavior.

Progress in understanding recovery from CNS injury should accelerate with advances in methods of behavior analysis. However, researchers and practitioners should exercise caution when interpreting the data in animal studies. Treatment-related enhanced recovery of sensorimotor behavior might be based on processes other than CNS repair per se, even when the improvement is correlated with measured changes in neural physiology and anatomy. Extrapolating the clinical significance of observations showing even large treatment-related changes in motor function in animal models without addressing the potential pitfalls is not a trivial matter. Intervention strategies may wind up in clinical trials and ultimately fail to yield beneficial effects in people. The animal model might then be viewed as being too distant from humans in physiology and anatomy when, instead, a more careful analysis of the intervention would not necessarily have led to predicted efficacy [22,23].

MULTIPLE INTERACTIVE PROCESSES CONTRIBUTE TO RESTORATION OF FUNCTION

CNS injury is followed by several broad categories of complex processes that might be promoted or mitigated by promising treatments, thereby mediating improved outcome. These processes overlap temporally and interact with each other [18,24–28]. Most research programs target brain repair mechanisms or neuroprotection, but restoration of function can depend almost totally on other mechanisms. Disentangling these processes and deciding which ones, if any, are linked to the treatment strategy is a formidable task that is rarely approached or even addressed by experimenters. It is important, however, to understand the possible contributions to improved function.

For example, a behavioral or biological treatment may increase motor performance in an animal model by enhancing motivational, attentional, or motor learning processes. Drugs such as catecholamine agonists are recognized for their ability in the intact animal to improve these processes [29], perhaps by making the task more salient [30]. Amphetamine and other catecholamine agonists, for example, have been used to facilitate performance in stroke and other models [31–36]. Moreover, after injury, brain regions needed for adequate motor learning may be functionally suppressed, either transiently or chronically. Some drug interventions may work by resolving neural shock to nearby or remote sites, rather than facilitating regeneration, repairing damaged axons, or preventing secondary degeneration.

With drug treatment, the animal with thoracic-level spinal injury may learn more quickly how to orient the forequarters such that the hindlimbs are better positioned to step in coordination with the forelimbs, as guided by vibrissae. Or, the functional depression of rostral sensory and motor areas in the spinal cord, and of the brain input interface within these regions, might be alleviated more rapidly with pharmacotherapy. Since the forequarters are involved in modulating hindlimb walking, this could permit more practice for hindlimb stepping in the home cage, thus improving overall performance. Additionally, the increased locomotor experience may activate use-dependent endogenous trophic factor expression, neuronal growth, or structural changes. These might be erroneously attributed to the original biological treatment, which in fact may not have instigated the key

phase of the performance change specifically. One potential consequence of not knowing this at the preclinical level might be that when the treatment eventually comes to the clinic, no benefit is detectable, depending on how outcome is measured and how much rehabilitative effort has already been devoted to maximizing residual function. If, in the animal model, forequarter function is involved preclinically in a treatment's effect, it is unclear how this would translate to upright walking in people. In other words, it is again important to make the distinction between behavioral compensation and true recovery, and also to determine how the details of compensation might translate from research animals used in preclinical studies to humans, who are also known to use compensatory strategies following damage [31].

BEHAVIORAL MODULATION OF NEURAL REPAIR MECHANISMS

Ideally, a treatment would fix the damage rather than simply facilitate motor learning. Repairing the damage might include replacing tissue that is lost, repairing tissue that remains but is partially damaged, reconnecting severed connections, or enhancing endogenous mechanisms that are involved in regeneration or cell replacement [27,37,38]. Moreover, the injury may create fertile conditions for motor enrichment to activate plasticity mechanisms such as neural or astrocytic growth factor expression, axonal sprouting, synapse remodeling, receptor density changes, neural-glial interactions, and cell mitotic activity, differentiation, and migration [18,24,28, 39–45].

Acute damage to the CNS in rats is often followed by slow degeneration of adjacent and remote tissue that can last for weeks or even months. The degeneration in focal cortical injury models can be exaggerated by behavioral manipulations started early after the injury, but regardless of the extent of the additional tissue loss, it is virtually undetectable for over a month [46]. Behaviorally, long-term degeneration and brain plasticity mechanisms may counteract each other, obscuring detection of both. The timing and intensity of motor enrichment manipulations appear to be critical factors. To our knowledge, there have been no studies of the effects of delayed motor therapy on the long-term slow degeneration of cells that occurs following ischemic or traumatic brain injury, or on the delayed degeneration that occurs when tissue is spared by brief cooling of the brain or by N-methyl-D-aspartate (NMDA) antagonists. It is reasonable to expect that secondary degeneration of neurons might be attenuated by intense behavioral demand if the early vulnerable period is avoided. Indeed, a recent report of rats sustaining striatal hemorrhage indicated that a daily regimen of exercise, alternating with intermittent immobilization of the nonimpaired forelimb beginning 8 days after the initial insult, rescued neurons from delayed chronic degeneration [47]. It is very difficult to know, without unbiased stereological analysis of many regions of the brain at multiple time points, whether a motor treatment is optimally beneficial. Even when outcome is improved, the functional measures may not target precisely brain tissue that might have been damaged by early behavioral manipulations.

It is therefore important to be particularly cautious about rehabilitation treatments that show beneficial or nondetrimental effects that are not verified by careful histological analysis. The logic behind the assumption that improved functional outcome from a treatment means that the treatment is not accompanied by undetectable tissue damage is faulty. An increase in the size of the primary injury does not necessarily lead to a worse outcome in many behavioral tests for which performance improves with repeated testing and practice. In fact, when behavioral rehabilitation is given to a group of rats with large lesions but not to a group with smaller lesions, the group with the larger lesions can perform better than the less injured, nonrehabilitated group on many types of motor tasks.

BEHAVIORAL REVERSAL OF PROGRESSIVE PARKINSONIAN DEGENERATION

Exercise and related motor-enrichment procedures have been shown to reduce degenerative events or promote sprouting of remaining terminals in slow degeneration models of Parkinson's disease [3,5,24]. To force use of the impaired forelimb, the rats were fitted with plaster of paris "vest" casts that encased the upper torso and nonimpaired forelimb during the first week after exposure to the dopamine-cell neurotoxin. This manipulation resulted in protection against vibrissae-evoked placing deficits (**Table 1**), akinesia (**Table 2**) and other sensorimotor deficits. Dopamine content in the striatum was also preserved (**Table 3**), along with other markers of the

Table 2.
Self-initiated stepping is impaired in the forelimb contralateral to nigrostriatal dopamine depletion, an asymmetry that is ameliorated by constraining the nonimpaired forelimb during the first 7 days after neurotoxin exposure. Lower score means less impairment in the "bad" forelimb (i.e., the limb corresponding to striatal degeneration).

Model	Impairment Scores		
	Day 14	Day 21	Day 28
Sham	0 ± 0.1	–5.3 ± 1.2*	3.1 ± 1.1
6-OHDA, no cast	63.0 ± 7.2*	64.1 ± 1.4*	63.9 ± 4.6*
6-OHDA, cast, days 1–7	7.1 ± 3.2	1.4 ± 3.8	9.6 ± 2.1
6-OHDA, cast, days 7–13	51.3 ± 3.7*	72.4 ± 5.1*	79.6 ± 8.3*
6-OHDA, cast, days 3–9	10.1 ± 4.7*	20.0 ± 13.6*	41.6 ± 12.1*

*Statistically significant difference from baseline measurements.
Note: Each limb was tested separately, in isolation from the other forelimb and hindlimbs. Data are mean ± standard error of the mean steps per minute made with the nonimpaired forelimb minus steps per minute made with the impaired (parkinsonian) forelimb when the animal is supported solely on that limb [4,5].

Table 3.
Dopamine levels in the striatum are spared by early (days 1–7), but not by late (days 7–13), forced use of the impaired forelimb.

Model	Dopamine Levels (%)
Sham	103 ±11
6-OHDA, no cast	30 ± 8*
6-OHDA, cast, days 1–7	81 ± 9
6-OHDA, cast, days 7–13	23 ± 13*
6-OHDA, cast, days 3–9	62 ± 17*

*Significantly less than sham group.
Note: Data are percentages of striatal dopamine remaining relative to intact hemisphere [4,5].

integrity of striatal dopamine terminals [5]. Waiting until the second week to impose forelimb use was not effective. Treadmill exercise during the first week after neurotoxin exposure (which has also been studied in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model) also had beneficial behavioral and neurochemical effects [3]. If the toxin levels are too high, however, which causes degeneration to occur to rapidly, forced forelimb use is ineffective. Motor enrichment methods may work in the partial-injury Parkinson model because glial-derived neurotrophic factor (GDNF), fibroblast growth factor 2 (FGF-2), brain-derived neurotrophic factor (BDNF), and other trophic factors are upregulated by motor enrichment [48–53] and have time to work. The implications for people with Parkinson's disease are that early, presymptom detection using more sensitive behavioral and neuroimaging techniques will be required to identify candidates for exercise intervention. Symptoms of Parkinson's disease usually present unilaterally before progressing to both sides of the body. The side of the body that does not show obvious symptoms likely reflects a lower subclinical level of degeneration in the corresponding hemisphere, which may make dopamine cells there more salvageable with behavior-based treatments.

CONCLUSIONS

It is a time to be both optimistic and cautious about research in CNS injury. Considerable progress has been made in the development of neurological tests and in understanding how motor experience promotes neural events linked to restoration or maintenance of function in models of stroke, parkinsonism, traumatic brain damage, and spinal cord injury [28,31,53–58; and see other papers in this issue]. The extent to which training, together with interventions that promote CNS repair or prevent delayed degeneration of neurons, might enhance brain-dependent behaviors should be carefully investigated preclinically. Behavioral tests and histological methods aimed at evaluating the connections between the brain and spinal cord should be included in this research, as well as measures of voluntary initiation of overground or vertical/lateral forelimb stepping and other movements associated with central control of spinal neurons [18,19,39,57,69]. In addition, standard tests for spinal cord function and techniques that target the hindlimbs [66–68] should continue to be used and improved. The possibility that an intervention improves performance mainly by facilitating the learning

of compensatory motor tricks should not be dismissed [18,39,57,69]. To transfer promising biological treatment strategies to the level of the clinical trial more successfully, behavior-brain interactions must be taken into account, and the influence of physical rehabilitation, or its absence, should be explored more thoroughly [70].

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