

The interplay between behavior and neurodegeneration in rat models of Parkinson's disease and stroke

Martin T. Woodlee^a and Timothy Schallert^{a,b,c,d,*}

^a*Institute for Neuroscience, The University of Texas at Austin, Austin, TX, USA*

^b*Department of Psychology, The University of Texas at Austin, Austin, TX, USA*

^c*Department of Neurosurgery, University of Michigan, Ann Arbor, MI, USA*

^d*Henry Ford Health Science Center, Detroit, MI, USA*

Abstract. The effects of extreme disuse or overuse of the limbs in rat models of Parkinson's disease and stroke are discussed. In unilaterally lesioned rats, immobilizing one forelimb in a cast forces complete disuse of this limb and extreme overuse of the uncasted limb. This procedure has diverse effects on histological and behavioral outcomes in these models, depending upon how and when it is applied relative to the lesion. Effects on behavioral outcome, post-lesion plasticity events, and expression of trophic factors are discussed. The effects of forced disuse or overuse vary among lesion types and can include neuroprotection, changes in synaptogenesis, or even exaggeration of tissue loss. The diversity of behavior-driven structural changes in the brain underscores the potential importance of carefully tailoring physical restorative therapy to specific neurological problems in order to optimize outcomes. In addition, we stress the need to recognize the reciprocal influence that behavior and the brain can have upon each other.

Keywords: Parkinson's disease, stroke, constraint therapy, trophic factors, rehabilitation, casting, use-dependency, plasticity

1. Introduction

Physical rehabilitative therapy is gaining recognition as a valuable therapeutic option for treating many neurological maladies, including stroke, spinal cord injury, and Parkinson's disease. Despite the apparent effectiveness of physical therapy, however, there is a relative dearth of controlled studies examining how the timing, type, and intensity of such treatments can affect functional and pathological outcomes. One notable exception is the work of Taub and colleagues (see V.W. Mark and E. Taub, this issue) investigating constraint-induced therapy in chronic stroke patients.

Given the cascade of events that occur in the acute stages of stroke [23], it may be valuable to consider whether early rehabilitative therapy would be useful and, if so, the best way to apply it. In this paper we review evidence generated in rat models of stroke and parkinsonism that demonstrates use-dependent effects resulting from an extreme form of physical therapy. The effects of this therapy vary according to the type of lesion model used, when the therapy is applied relative to the lesion, and, in unilaterally lesioned animals, which hemisphere is targeted.

2. Studying use-dependency in rats: techniques and considerations

2.1. Behavioral testing

The rat makes an excellent model system for studying motor disorders [9]. A wide variety of sensitive

*Corresponding author: Timothy Schallert, Ph.D. Department of Psychology The University of Texas at Austin 1 University Station, #A8000 Austin, TX 78712, USA. Tel.: +1 512 471 6141; Fax: +1 512 232 4335; E-mail: tschallert@mail.utexas.edu.

behavioral tests have been developed to evaluate motor and cognitive dysfunction caused by nervous system insult in rats, many of which correlate well with histological outcomes [48,54,55,62]. When applied appropriately, such tests can determine the location and extent of brain lesions in rats. These behavioral data, when combined with histological examinations, can provide a more meaningful picture of an experimental therapy's potential real-world effectiveness than can histology alone. Two behavioral tests used frequently in our lab, and referred to in the following sections, are the limb-use asymmetry test (a.k.a. the "cylinder test") and vibrissae-elicited forelimb placing. These are described briefly below. For more methodological detail on these tests and several others useful for evaluating sensorimotor function, see [55].

In the limb-use asymmetry test, rats are placed in a transparent Plexiglas cylinder and observed as they rear and use their forelimbs to explore the inner wall [48]. Rats may use one or both limbs for postural support and weight-shifting or lateral-stepping movements along the inside of the cylinder. The number of independent limb uses for both the ipsilesional and contralesional limbs is recorded, as is the number of simultaneous ("both") limb uses. A composite score of percent limb-use asymmetry can be calculated from these data which correlates well with lesion extent and is very sensitive to small lesions other tests may be unable to detect [59, 62].

In the vibrissae-elicited forelimb placing test, the rat is held with all four limbs suspended in the air and moved slowly towards a tabletop by the experimenter [55]. The forelimb not being tested is restrained by the experimenter as he brushes the rat's side or chin vibrissae against the table's edge, eliciting a forelimb placing response in normal animals. Lesioned animals will typically fail to place on the contralesional side, and the severity of the deficit can be recorded as percent successful placing out of ten trials. Relative to the cylinder test, a greater extent of damage to the sensorimotor cortex or striatum is typically required to produce deficits in this test. In addition, we have developed a new variant of this test which involves turning the rat on its side and eliciting placing by stimulating the vibrissae opposite the limb being tested, in order to test across the midline. Preliminary work in our lab has shown that different motor system lesions produce different deficit patterns on this test when cross-midline placing is also examined [55]. Indeed, extensive ischemic damage to the striatum produces a pattern of behavioral deficits on this test which is qualitatively distinct from that seen following dopamine-specific nigrostriatal degeneration [65].

2.2. *Forced-use and rehabilitative techniques*

Several techniques have been developed to encourage motor rehabilitation in rats. Commonly used methods include acrobatic training [5], environmental enrichment [25], and treadmill or wheel running [60,63]. The manipulation used in many of our studies is casting, which, except in regard to its intensity and the constant nature of its application, is analogous to the constraint therapy used by Taub and others to overcome the "learned non-use" of the impaired limb seen in stroke sufferers (see V.W. Mark and E. Taub, this issue). Anesthetized rats are fitted with plaster of Paris casts that immobilize one forelimb while allowing full range of motion in the other limb. Control casts that allow the use of both limbs may also be used. Casting represents a drastic form of use manipulation: one limb is completely disused while the other, which must be used for all of the rat's usual activities (e.g., exploratory rearing, grooming, feeding), is subject to extreme overuse. It is important to note, though, that the effects of casting which we review below do not appear to result from increased stress, since unilaterally lesioned animals have similar corticosterone levels regardless of which limb (i.e., impaired or unimpaired) is restrained; yet the choice of restrained limb yields greatly different outcomes as described below [8,53]. Casting also does not lead to core hyperthermia [19, 28], which is an important consideration given the role that increased temperature has been shown to play in the evolution of ischemic damage [24].

The above methods involve altering the use of motor circuitry. Opportunities also exist for studying forced-use effects in sensory systems. For example, O'Dell and Marshall found that methamphetamine-induced neurotoxicity in the barrel fields of rat sensory cortex was attenuated when the contralateral vibrissae were removed [41]. The authors suggest that the excessive whisking (and therefore increased sensory input from the vibrissae) which occurs under the influence of methamphetamine may contribute to use-dependent degeneration of the corresponding cortical sensory neurons which receive the increased input.

3. **Effects of disuse and overuse in stroke models**

We and others have investigated the effects of casting and other kinds of motor use manipulations in rats during various time frames following unilateral electrolytic damage to the forelimb area of the sensorimotor cortex

(FL-SMC), as well as following middle cerebral artery occlusion (MCAo; a stroke model) procedures which predominantly affect motor cortical areas [7,8,27,28,31,35,37,39,44,52,53]. When the ipsilesional forelimb is immobilized for one week following a lesion, thereby forcing reliance on the impaired limb, two noteworthy events occur. First, there is a use-dependent exaggeration of the primary insult, such that the lesion area grows in size compared to that of uncasted rats or rats whose impaired limb is casted. This exaggeration of injury, which develops over many weeks following removal of the cast, is associated with somewhat more severe and enduring deficits in the cylinder and placing tests described above [35]. Secondly, there is a reduction in the enhanced layer V dendritic arborization normally seen in the homotopic (unlesioned) motor cortex following unilateral injury. These plastic changes are discussed in more detail in Section 5 below.

The increased vulnerability of peri-lesion tissue to behavioral demand seems to disappear after an early period following the cortical insult. Exaggeration of the lesion is not apparent when casting of the unimpaired limb is delayed until the second post-lesion week [28]. Nevertheless, delayed casting can interfere with restoration of function relative to uncasted animals, as measured in the cylinder test. Additionally, the effect appears to be dependent upon the lesion site: no exaggeration of either injury or behavioral impairment occurs following MCAo techniques that primarily affect striatal areas while sparing cortical tissue [7].

As noted earlier, use-dependent exaggeration of injury cannot be attributed to systemic hyperthermia or stress secondary to casting of the unimpaired limb, especially since casting of the impaired limb does not have such marked effects [35]. Further evidence against systemic mechanisms comes from a study by DeBow et al. [19] showing that when rats were simultaneously given unilateral lesions of motor and visual cortices, only the motor cortex lesion was enlarged by constraining the unimpaired forelimb. It is possible that the exaggeration is related to use-dependent local vascular or thermal changes [19], or to increased levels of extracellular glutamate in the hemisphere corresponding to the overused limb. Indeed, glutamate and the N-methyl-D-aspartate (NMDA) glutamate receptor are known to be involved in the excitotoxic cascade which follows ischemic damage [23], and the administration of NMDA receptor antagonists such as MK-801 in the early phases after ischemic injury can be neuroprotective against the exaggerated cell loss [27]. Bland et al. [6] found that extracellular glutamate levels mea-

sured by microdialysis during exploratory movement in casted rats were greater in the motor cortex corresponding to the overused limb and suppressed in the hemisphere corresponding to the casted limb. Humm et al. [27] administered MK-801 to ipsilesionally casted rats following electrolytic damage to the FL-SMC, and this spared neural tissue and enhanced recovery of function relative to vehicle-injected casted controls. That is, MK-801 blocked use-dependent exaggeration of the injury. This is in contrast to the functionally detrimental effects of MK-801 administered later after the injury, as discussed below in the section on plasticity.

Different effects are seen when the *impaired* limb is casted following cortical damage. When this is done, there is no exaggeration of the primary insult, and only slightly poorer performance on behavioral tests is observed [35]. This outcome provides additional evidence that systemic events related to limb immobilization are likely not responsible for exaggeration of the injury. However, if the impaired limb is casted during the first week after injury, and then subsequently overused during the second week by switching the cast to the other limb, use-dependent exaggeration of the injury becomes apparent [39]. Thus, complete disuse of the impaired limb appears to extend the window of vulnerability to later overuse. For a summary of these use-dependent effects following cortical damage, see Fig. 1.

Altogether, the message from these studies is that in rat models there is an early window of vulnerability following cortical damage when excessive behavioral pressure may compromise weakened peri-lesion tissue that might have otherwise survived. Nevertheless, complete disuse of the impaired limb after injury does lead to mildly worse outcomes, and may only shift the window of vulnerability to a later time point. Therefore, we suggest that graded motor rehabilitative therapy, which starts out very mildly, may provide for optimal outcomes. Indeed, *intermittent* early constraint therapy combined with mild motor rehabilitation appears to protect against delayed slow degeneration of tissue in brain regions remote to an insult [18]. The details of the intensity and appropriate timing of such therapy in different lesions and across different species merits further study.

4. Effects of disuse and overuse in models of Parkinson's disease

Use-dependent effects in Parkinson's disease (PD) appear to be markedly different than what is seen with

Lesioned animals [†]			Behavioral outcomes	Peri-lesion (ipsi) cortex events	Contra-lesion cortex events
	C		mild ↑ in deficits & asymmetry	↓BDNF expression	--
		I	↑behavioral deficits & asymmetry	--	--
	I		↑behavioral deficits & asymmetry	↑lesion size	↓lesion-induced plasticity
	C	I	↑behavioral deficits & asymmetry	↑lesion size, ↓BDNF expression	--
Sham animals*			Behavioral outcomes	Ipsi-cast cortex events	Contra-cast cortex events
			transient mild limb-use asymmetry	↑corticocellular glutamate	↓corticocellular glutamate
0	7	14	days post-lesion		

C = contralesion (impaired) limb casted
I = ipsilesion (unimpaired) limb casted

[†] effects relative to lesioned but uncasted animals
^{*} effects relative to uncasted animals

Fig. 1. Relative effects of casting on animals receiving unilateral electrolytic damage to the FL-SMC. Note that when one limb is casted (i.e., disused), the other is overused. Intense early overuse of the impaired limb leads to greater impairments and/or increased lesion size depending on the time frame of the casting. The window of vulnerability for these overuse effects can be extended by forcing disuse of the impaired limb early after injury. Early disuse of the impaired limb (without subsequent overuse) has only a minor effect on behavioral outcome.

cortical damage. Infusions of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB) of rats destroy dopaminergic axons projecting to the striatum and their cell bodies located in the substantia nigra (SN). These infusions are often made unilaterally to produce a hemi-Parkinsonian rat capable of feeding, drinking, grooming, and moving. Loss of SN cells is the pathological hallmark of PD, and rats treated with 6-OHDA display many of the same symptoms as human PD patients, including bradykinesia, rigidity, and sometimes even resting tremor (see movies on our website, www.schallertlab.org; [9]).

In rat models of PD, most motor symptoms generally do not become evident until dopamine (DA) levels are depleted by approximately 80%, though sensitive behavioral assays such as the cylinder test may be able to detect smaller depletions [54,57,62]. Tillerson et al. [61] found use-related effects when they casted the affected forelimb of rats at various time points following unilateral administration of 6-OHDA. After injecting rats with 6-OHDA at concentrations that would only deplete DA levels by 20% in uncasted rats, the experimenters casted the animals' contralateral forelimbs for seven days. When tested after cast removal, these rats displayed significant behavioral asymmetries in limb use in the cylinder. Upon post-mortem assay, it was discovered that the rats had suffered an exacerbation of the neurochemical damage to the tune of a 60% DA depletion [61].

In contrast, rats subjected to 6-OHDA doses that would usually produce up to a 90% DA depletion (and thus rather severe Parkinsonian signs in the affected limb) and subsequently forced to overuse the affected limb showed virtually no limb-use asymmetry and no detectable impairments in the affected limb for the 60 days following cast removal during which they were observed [62]. These animals also showed marked sparing of striatal DA levels. This use-dependent protection was attenuated if casting was initiated 3 days following the 6-OHDA injection, and was altogether absent when casting was started 7 days post-injection. Casting had no beneficial effect, however, in animals which were more severely depleted (i.e., greater than 90% DA loss). Also, when forelimb function was thus spared, casting the affected limb later (during the second or third week post-lesion) resulted in severe functional deficits and chronic DA depletion [61]. For a summary of these use-dependent effects in the 6-OHDA lesion model, see Fig. 2.

Thus, the protection against 6-OHDA neurotoxicity afforded by extensive limb use is "fragile", and subject to disruption by future disuse. Clinically, this may indicate that it is important for physical therapy regimens for parkinsonian patients to be continuous, since gains made during the course of therapy may be lost if and when patients return to a sedentary lifestyle.

It is important to note that these effects were found in the 6-OHDA rat model of PD, which diverges in

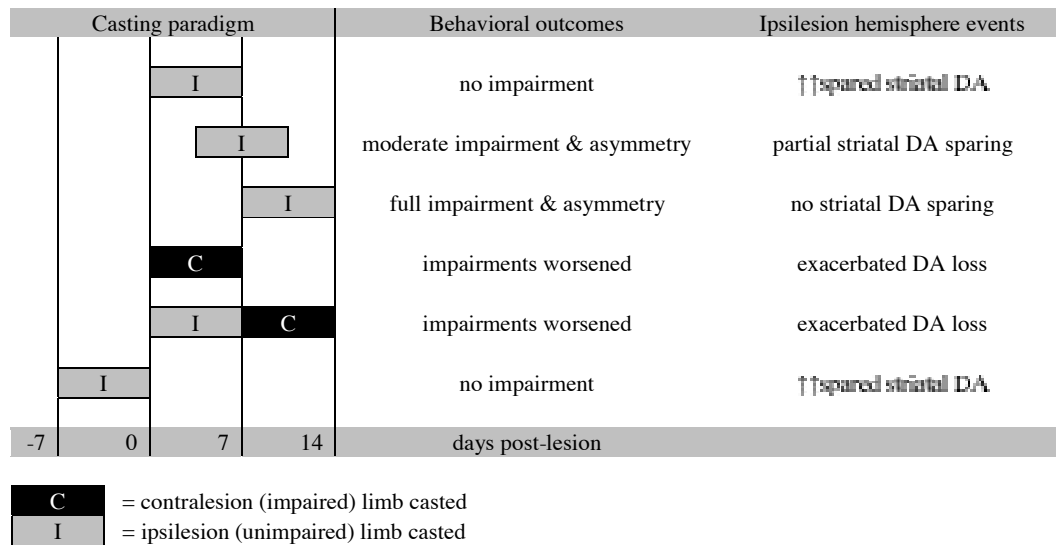


Fig. 2. Effects of casting on animals receiving unilateral 6-OHDA in the MFB, relative to uncasted animals. Note that when one limb is casted (i.e., disused), the other is overused. Overuse of the impaired limb around the time of lesioning ameliorates the 6-OHDA induced deficits in a time-dependent manner. Limb function may still be vulnerable to future disuse, however. Disuse of the impaired limb after lesioning exacerbates the behavioral and neurochemical deficit.

many respects from the clinical picture of a human PD patient. Most notably, 6-OHDA is usually delivered as a single unilateral dose which then rapidly proceeds to kill DAergic neurons on only one side of the brain. It largely remains to be seen whether use-dependent effects would persist in other models of PD such as the bilateral MPTP mouse or primate models, or in models that could conceivably reproduce the long-term degeneration of DA neurons typical of human PD (e.g., administration of the pesticide rotenone via subcutaneous minipumps [56] or intrastriatal infusion of escalating doses of 6-OHDA [22]). Tillerson et al. found, however, that MPTP-treated mice showed less behavioral impairment and greater sparing of striatal DA if they were exposed to treadmill running for the first ten days post-lesion [60], indicating that use-dependent effects are likely to be present in other models of the disease. The refinement of clinically relevant animal models of PD is an important issue and the interested reader is referred to [3,9,17,42] for reviews.

5. Use-dependent effects on plasticity and growth factors

5.1. Lesion-induced plasticity and behavior-brain interactions

A number of studies have investigated neural plasticity events subsequent to brain lesions (see [32] for

review). Early after unilateral electrolytic lesions of the FL-SMC, rats come to rely heavily on the ipsilesional limb to carry out their daily activities. Following such lesions, there occurs a time-dependent increase in dendritic arborization in layer V of the homotopic (unlesioned) cortex [30]; see also [4]. This enhanced arborization is greatest at 18 days after this type of lesion, after which there is a partial “pruning back” of the dendritic arbors. The number of multiple synaptic boutons and perforated post-synaptic densities in this area also increases [29]. Such synapses are similar to those formed as a result of long-term potentiation (LTP) induction, which is a well-known cellular-level model of learning. Thus, these plastic changes may represent the neural substrate underlying new learning on the part of the undamaged motor cortex.

Such changes are closely associated with, and can be influenced by, behavioral events. In uncasted animals, the enhanced arborization corresponds in time with the period of disuse in the forelimb contralateral to the lesion, while the pruning phase is reflected behaviorally by a return to more symmetrical limb use [31]. Casting the contralesional forelimb has no effect on this plastic response, indicating that the partial recovery from motor asymmetry is not the cause of the pruning. However, when the ipsilesional forelimb (i.e., the forelimb corresponding to the intact motor cortex) is immobilized, the increases in dendritic arborization are attenuated and, as described earlier, histological and functional out-

comes suffer. Moreover, sham-operated rats forced to use only one forelimb do not display detectable plastic changes [31]. Thus, neither overuse alone nor a lesion alone lead to these changes—rather, a behavior-brain interaction is involved. It is possible that brain injury upregulates neurotrophic factors that prepare the brain for behavior-dependent structural changes [10,52,53].

5.2. *The relationship to motor compensation*

Because these plastic changes appear to occur only in the presence of over-reliance on the intact limb (caused either naturally by relative disuse of the impaired limb, or artificially by casting), they may reflect learning mechanisms which allow the intact cortex to guide the intact limb in making compensatory movements. Following unilateral motor system lesions, rats and other animals display a remarkable capacity to adapt to the deficit by using remaining systems to approximate compromised motor behaviors [46,55,64]. One important (and often overlooked) corollary to this fact is that if behavioral tests are meant to be indicative of true brain repair or neuroprotection, the outcome scores must reveal the deficit rather than hide it because the test is unduly susceptible to compensatory tricks. One test that illustrates this problem is the ledged tapered beam test [55]. Rats tested for hindlimb foot faults (i.e., slips) while traversing a narrow beam 450 days after MCAo injury appear to be recovered; that is, they can run the beam quickly without slipping. If a ledge is added along either side of the beam, however, these animals will begin to display foot faults (control animals typically do not) [47,55]. The ledge acts as a “crutch” that allows the rat to display its deficit without slipping or pausing. Many behavioral tests currently in use may be prone to confounding by compensatory adaptations. This is not necessarily a drawback if the goal is to examine the animal’s ability to learn compensation; indeed, it might be interesting to study whether the mechanisms underlying such learning are offline for a time after certain lesions. But, in general, one must be very careful in the choice and design of behavioral tests, especially when asking questions about true brain repair or recovery (versus “replacement”) of function.

Additional evidence suggesting that new motor learning may have more to do with “recovery” than does true brain repair comes from experiments with the NMDA antagonist drug MK-801. As noted earlier, MK-801 administered early after ischemic damage can act as a neuroprotectant, possibly by dampening the post-ischemic excitotoxic cascade involving NMDA re-

ceptors [1,2,27]. The NMDA receptor plays a crucial role in the induction of LTP and is therefore hypothesized to be involved in learning [40]. When MK-801 or ethanol (which can essentially act as an NMDA antagonist) is administered to apparently recovered rats late after cortical injury, a dramatic reinstatement of placing deficits and limb-use asymmetry occurs which lasts well beyond the half-life of the drug [34,36]. Reinstatement of functional deficits caused by hypoxic-ischemic lesions sustained during the neonatal period can also be elicited by administering NMDA antagonists when the animal reaches adulthood [21]. Furthermore, the phase of dendritic pruning in the homotopic cortex, which is associated with a return to more symmetrical limb use following unilateral lesions, can be blocked by MK-801 or ethanol [34,36].

Reinstatement of deficits may also be triggered by a variety of other drugs, including benzodiazepines and noradrenergic antagonists [38,50,58]. The topic of fragile recovery and reinstatement of deficits in response to drugs and environmental triggers is a complex one that is underappreciated, understudied, and potentially extremely important (see Feeney et al., this issue, for more in-depth coverage of these issues).

5.3. *Use-dependent changes in growth factor expression*

Following electrolytic damage to the FL-SMC in rats, an increase in astrocytes expressing basic fibroblast growth factor (bFGF) and glial fibrillary acidic protein (GFAP) can be observed in the peri-lesion area [45]. When these increases in bFGF are blocked with neutralizing antibodies, dendritic arborization and spine density are reduced in peri-lesion layer V pyramidal neurons compared to controls, and recovery is retarded [45]. Casting the impaired limb dampens the bFGF spike without affecting post-lesion GFAP expression [51]. This effect suggests that some use of the contralateral limb may be necessary to allow the increase in bFGF and, therefore, to maintain the integrity of remaining neurons around the lesion. It may also explain the observation that casting of the impaired limb for the first week or two following the injury leads to modest disruption of functional recovery in that limb [35]. In addition, as noted earlier, disuse during the first week followed by overuse during the second week causes exaggeration of the injury [39], which may result from excessive behavioral demand on a background of down-regulated bFGF. That is, the “shift” of the post-lesion window of vulnerability discussed earlier may be re-

lated to downregulation of trophic factors in the hemisphere corresponding to the disused limb.

Another trophic factor, glial cell line-derived neurotrophic factor (GDNF), has been shown to be neuroprotective against 6-OHDA insult when delivered into the striatum or substantia nigra of rats via an adenoviral vector [11,15,16,33]. Cohen et al. [12] studied the effects of casting on expression of GDNF and found that levels were temporarily increased in the striatum contralateral to the overused limb. In this same study the authors also found that forcing limb overuse for one week before 6-OHDA challenge was neuroprotective. Thus, both pre- and post-lesion casting can have a protective effect, which may be due in part to the endogenous upregulation of growth factors that have been directly shown to be protective when applied by more invasive means.

6. The importance of proper timing and intensity

The evidence presented here demonstrates that behavioral manipulation in the form of physical therapy can interact quite dynamically with ongoing post-lesion degenerative and plasticity events, as well as growth factor expression and the lesion-induced behavioral deficits themselves. It is therefore important that such therapy be properly tuned to the type and extent of lesion and, in some cases, that it be applied appropriately to different sides of the body (e.g., in cases of unilateral stroke affecting the motor cortex) [49]. We have shown that in stroke models, behaviorally stressing weakened tissue too soon after the primary injury can lead to more extensive delayed degeneration and greater deficits; but, then, complete disuse of the impaired limb still results in some retardation of the recovery process. Thus, for stroke, it would seem that the optimal rehabilitation schedule would be one that starts slowly and becomes more aggressive once the window of vulnerability has passed.

It is not known if similar effects would be found for ischemic damage affecting other areas. Some evidence exists indicating that hippocampal lesions may not be subject to this sort of exaggeration of injury [13]. In this study, however, the application of behavioral demand was delayed until the fourth postoperative day, by which time the window of cellular vulnerability may have passed. Additionally, Farrell et al. [20] have found that environmental enrichment initiated early after ischemic injury can lead to death of hippocampal cells.

In contrast to ischemic damage, the picture for Parkinson's disease (which itself progresses slowly) is of a "use-it-or-lose-it" situation. In parkinsonian animal models, if physical therapy is to be maximally effective in preventing neuronal terminal loss, it must be started very early after (or even before) the insult and consistently maintained for an unknown period of time. The precise etiology of PD is not known; although environmental neurotoxin exposure probably accounts for some cases, evidence also suggests a contribution from genetic factors (see [3] for review). It is not known if physical therapy would be useful when genetic factors are the cause, though if the mechanism of neuroprotection involves upregulation of trophic support, there is reason to hope that this may be the case. In addition, motor therapy can have beneficial effects in PD patients even after symptoms surface [14,26,43].

7. Conclusions

The classical view that changes in the brain lead to changes in behavior must be revised. Though this is part of the picture, it is certainly also true that behavioral demand can have a great deal of influence on the brain. Recognition of this reciprocal interaction will open the door for research opportunities with clear clinical significance. Mechanisms of plasticity, expression of endogenous trophic factors, and the progression of recovery can all be manipulated by applying behavioral pressure in specific ways and at specific time points in relation to the neural insult. An investigation of how behavioral manipulations and rehabilitative strategies interact with different kinds of brain injury should yield improved therapeutic options while teaching us a great deal more about the brain's recovery processes.

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