

# Plasticity

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**Summary:** Over the past 20 years, evidence has mounted regarding the capacity of the central nervous system to alter its structure and function throughout life. Injury to the central nervous system appears to be a particularly potent trigger for plastic mechanisms to be elicited. Following focal injury, widespread neurophysiological and neuroanatomical changes occur both in the peri-infarct region, as well as throughout the ipsi- and contralesional cortex, in a complex, time-dependent cascade. Since such post-injury plasticity can be both adaptive or maladaptive, current research is directed at understanding how plasticity may be modulated to develop more effective therapeutic interventions for neu-

rological disorders, such as stroke. Behavioral training appears to be a significant contributor to adaptive plasticity after injury, providing a neuroscientific foundation for the development of physical therapeutic approaches. Adjuvant therapies, such as pharmacological agents and exogenous electrical stimulation, may provide a more receptive environment through which behavioral therapies may be imparted. This chapter reviews some of the recent results from animal models of injury and recovery that depict the complex time course of plasticity following cortical injury and implications for neurorehabilitation. **Key Words:** plasticity, learning, stroke, brain repair, motor systems, cortex.

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## INTRODUCTION

### What is plasticity and what are its implications for neurological rehabilitation?

Cortical plasticity is the capability of the cerebral cortex to alter its functional organization as a result of experience. As such, plasticity refers to the phenomenon of change, not to the specific underlying mechanisms. As early as the mid-1800s, it was suggested that surviving portions of the brain alter functional activity in a vicarious manner to provide a substrate for recovery. But it has only been in the past two decades that numerous correlates of plasticity have been demonstrated in experimental animal models as well as in human subjects, allowing us to begin to address underlying mechanisms.

Correlates of plasticity have been observed at various levels of analysis from molecular to synaptic to cellular to network and systems levels. In both normal and injured animals, cortical representational maps are altered,

synapses change their morphology, dendrites and spines grow and contract, axons change their trajectory, various neurotransmitters are modulated, synapses are potentiated or depressed, and, to a limited extent, new neurons differentiate and survive.

While these new findings in the past 20 years have been exciting, these events still represent little more than correlative phenomenology, at least with respect to understanding how the brain recovers function after injury. With few exceptions, these investigations have not determined what aspects of plasticity are associated with adaptive vs. maladaptive events, or which ones are epiphenomenal.

In addition, significant progress has been made in understanding what factors drive cortical plasticity in normal and injured brains. Physiological and anatomical changes are driven by natural sensory stimulation, skill acquisition, peripheral injury, central injury, exogenous growth promoting agents, exogenous neuromodulating drugs, and exogenous electrical/magnetic stimulation. These factors that appear to drive cortical plasticity may be especially significant with regard to understanding ways to promote recovery. Thus, this review will outline our current understanding of functional cortical plasticity.

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### EARLY STUDIES OF CORTICAL PLASTICITY: ENVIRONMENTAL ENRICHMENT AND ACTIVITY-DEPENDENT PLASTICITY

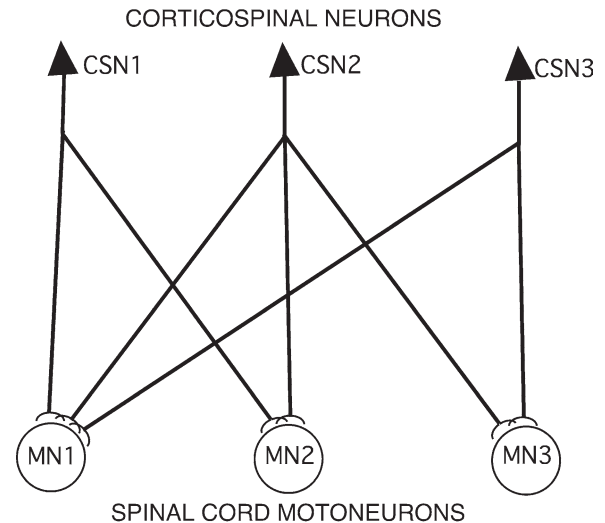
In all sensory and motor areas of the cerebral cortex that have been studied, significant functional and structural changes have been observed as a result of experience.<sup>1-6</sup> These studies largely evolved from environmental enrichment studies first postulated by Donald Hebb in the 1940s, and later characterized by Mark Rosenzweig and Marian Diamond in the 1960s.<sup>7</sup> These studies originally demonstrated that rats raised in enriched environments (EE) have larger brains and increased cortical thickness. Later it was shown that raising rats in EE resulted in larger neuronal cell bodies and nuclei, larger synaptic contacts, increased dendritic spine density, increased dendritic branching, and higher synapse to neuron ratio.<sup>8</sup> While changes appear to be larger and more rapid when rats are exposed to EE early in their development, by the 1960s it was shown that similar changes could occur in adult rats.<sup>9</sup> More recently, it was shown that enriched environments result in enhanced neurogenesis in the hippocampus of aged rats.<sup>10</sup>

One of the major advantages of the EE paradigm is that it can be implemented quite easily. But EE is a combination of complex inanimate and social stimulation.<sup>11</sup> It is composed of increased social interactions, sensory stimulation and physical activity. While novelty of the items is thought to play an important role (thus, playthings are replaced frequently), no single element has been isolated as the most important.

In the 1980s, a major paradigm shift in plasticity research gained popularity. In studies contributing to this change, specific aspects of sensory experience were manipulated experimentally to determine the effects on cortical receptive field properties. For example, when monkeys are trained to perform a sensory discrimination task with one or two digits, the representations of those digits enlarge, and the receptive field size decreases.<sup>12</sup> When two digits are sutured together, receptive field organization changes to reflect the synchronous input from the two digit surfaces.<sup>13</sup> This information led to a temporal correlation hypothesis that proposed that emergent properties in cerebral cortex are shaped by synchronous inputs and outputs.<sup>14</sup>

### ANATOMICAL SUBSTRATE FOR PLASTICITY IN MOTOR CORTEX

The demonstration of topographic plasticity in motor cortical representations has been a bit more problematic. This is primarily because normal functional representations in motor cortex are not the result of a simple mapping of receptor distribution onto the cortical sur-



**FIG. 1.** Convergence and divergence of cortical output pathways to motoneurons. Individual corticospinal neurons (CSN) branch to innervate multiple motoneuron pools (MN) in the spinal cord. Also, CSNs that innervate a particular MN pool are located in multiple sites within the motor representation in cortex. Finally, a dense network of intracortical fibers interconnects various cortical motor subregions (not shown). Thus, the motor cortex contains an anatomical substrate for topographic plasticity that may be engaged after focal cortical injury.

face, as are representations in sensory systems. Clearly, there is a global somatotopy such that lower extremities are represented in the most medial portions of M1, and upper extremities are represented in lateral portions of M1. Face and oral representations are represented more laterally still. Such somatotopy has been known since the 19<sup>th</sup> century. However, within local regions of the cerebral cortex, representations are highly overlapping. For example, the hand representation has been called a shared neural substrate for movement of the hand.<sup>15</sup> Individual corticospinal neurons branch to innervate several motoneuron pools.<sup>16</sup> The subset of corticospinal neurons that innervate a particular muscle are distributed over a large territory within the hand area, and overlap with corticospinal neurons innervating other motoneuron pools (FIG. 1). Add to this a dense network of local intracortical circuitry that interconnects various regions within the hand area,<sup>17</sup> and it becomes clear that the topographic organization of motor cortex is not simply based on muscle specificity, but on a somewhat more global grouping of functionally related muscles and joints.

One way of defining functional territories within the motor cortex of experimental animals is the use of microstimulation techniques in anesthetized preparations. In certain anesthetic states (e.g., under ketamine or propofol, but not barbiturates), muscle tone is maintained at a reasonably high level, and injection of a train of brief current pulses within the vicinity of the soma of the corticospinal neurons results in activation of descending

fibers, in turn resulting in muscular contraction. Typically, the muscles or joint movements activated by the lowest possible current levels define the functional representation at that site.<sup>18</sup> Clearly, there are other muscles represented at a given site, in the sense that there are corticospinal neurons that project to motoneuron pools not involved in the movement evoked at threshold. However, this procedure allows an objective way to track the “most represented movement” over time, after training and after injury.

### USE-DEPENDENT VERSUS LEARNING-DEPENDENT PLASTICITY IN MOTOR CORTEX

Motor training appears to alter cortical motor representations within just a few days.<sup>19,20</sup> As an animal practices a task, movements become increasingly stereotyped, and thus, the same subset of joint movements and muscle contractions are co-activated, or activated in close temporal continuity. Perhaps surprisingly, microstimulation after training results in more complex combinations of movements that evoke co-contraction of the same muscle subsets that are used in the behavioral task.<sup>19</sup> Thus, somewhat akin to the somatosensory cortex, temporal contiguity of specific joint movements results in an emergence of multi-joint modules in the motor cortex. This property is a result both of convergence of multi-joint inputs from somatosensory and motor cortex, as well as temporally contiguous outputs from cortical neurons.

A hypothesis has emerged suggesting that changes in motor cortical maps (and probably sensory maps as well) are driven by specific aspects of behavioral demand (i.e., skill acquisition), and are not simply the result of repetitive use. For example, monkeys required to extract food pellets from very small wells display gradual improvement in performance on the task. A typical asymptotic learning curve is demonstrated over the course of approximately 1 week. Training on this task results in the map changes noted above. It also results in various changes in neuronal morphology, including dendritic arborization, synaptogenesis, and dendritic spine length. However, if animals are exposed to a task that requires little or no learning, no changes in motor maps or neuronal morphology occur. For example, no map changes have been observed in monkeys required to retrieve pellets from a large well (a task that they perform optimally from the initial exposure to the task), motor maps remain stable.<sup>21</sup> The same type of results have been demonstrated in rats required to simply press a bar or undergo strength training.<sup>4,22</sup>

Thus, motor cortical plasticity in normal adult brains appears to be learning-dependent or skill-dependent, and

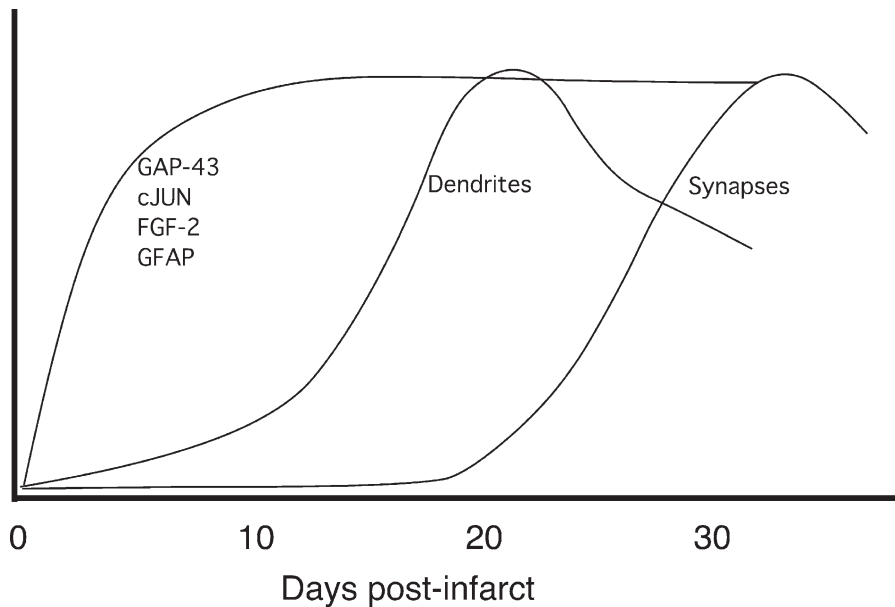
not simply use-dependent. If this phenomenon generalizes to injured brains, then rehabilitation techniques should be optimal if they induce increasing levels of motor skill. Repetitive use alone is unlikely to induce large-scale, long-lasting changes in cortical networks.

### LOCAL PLASTICITY AFTER LESIONS IN THE MOTOR CORTEX

Direct evidence that adjacent regions of the cortex function in a vicarious manner after injury can be traced to studies by Glees and Cole in the early 1950s.<sup>23</sup> In these studies, monkeys were subjected to local injury to the thumb representation (identified using surface stimulation techniques). When the brains were remapped following behavioral recovery, it was discovered that the thumb area reappeared in the adjacent cortical territory. Similar findings were observed after small ischemic lesions in the somatosensory cortex over 3 decades later.<sup>24</sup>

However, using intracortical microstimulation techniques in primary motor cortex, somewhat different findings were observed by Nudo et al. in the 1990s. Small, subtotal lesions were made in a portion of the hand representation in squirrel monkeys (about 30%), and the animals were allowed to recover spontaneously (i.e., without the benefit of rehabilitative training) for several weeks. In contrast to Glees and Cole’s earlier finding, the remaining hand area was reduced in size.<sup>25</sup> However, in animals that underwent rehabilitative training by restricting the less impaired limb, and training the impaired limb on a pellet retrieval task, the hand representation was preserved. In some cases the hand representation expanded into the adjacent elbow and shoulder representations.<sup>26</sup> In retrospect, it is quite possible that the re-emergence of thumb representations in Glees and Cole’s study may have been driven by post-injury behavioral demands.

In addition to alterations in functional maps in the peri-infarct tissue after experimental stroke, it is now clear that neuroanatomical changes occur as well. Between 3 and 14 days post-infarct, rats demonstrate increased GAP-43 immunoreactivity, suggesting significant neurite outgrowth in the peri-infarct region during this time period.<sup>27</sup> Then, between 14 and 60 days post-infarct, synaptophysin staining is significantly elevated, signifying increased synaptogenesis (FIG. 2).<sup>27</sup> Further, local, surviving neurons become hyperexcitable, with associated up-regulation of NMDA receptors and down-regulation of GABA<sub>A</sub> receptors. Recent evidence demonstrates that axonal sprouting occurs in the peri-infarct area.<sup>28,29</sup> Based on more recent data, a picture is emerging in the peri-infarct cortex of an evolving environment, in which growth inhibition is suppressed for about 1 month post-infarct. This period is followed by “waves”



**FIG. 2.** Sequence of anatomical changes in intact cortex after focal ischemic infarct. A time-dependent set of morphological changes is set into motion by focal ischemic damage to the cerebral cortex. Very early after injury, molecules associated with growth promotion, such as GAP-43, cJUN, FGF-2, and GFAP can be demonstrated. In the second to third week post-injury, significant dendritic sprouting can be observed in the contralesional hemisphere. Widespread synaptogenesis appears by the third week. This figure illustrates only a small number of events following focal infarct. For a more detailed picture see Carmichael et al. and Jones et al.<sup>58,59</sup>

of growth promotion which may modulate the brain's self-repair processes.<sup>30</sup>

### REMOTE PLASTICITY AFTER LESIONS IN THE MOTOR CORTEX

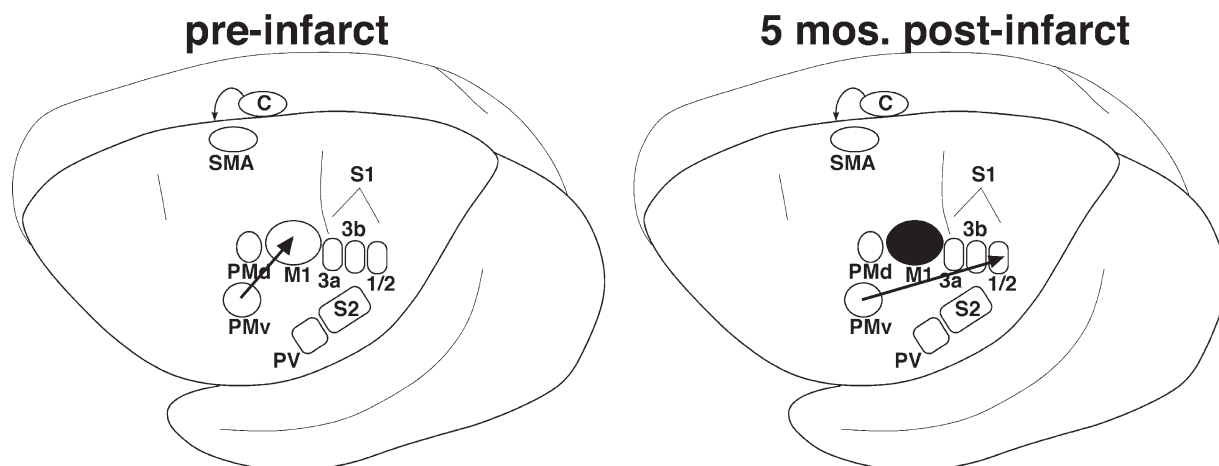
It is now clear that after stroke, neuroanatomical changes occur not only in the peri-infarct cortex, but also in remote areas, such as the contralesional hemisphere. In the first weeks after stroke, astrocytes proliferate and neurotrophic factors are expressed.<sup>31</sup> Neuroanatomical changes have been characterized in a number of studies and portray a time-dependent increase in dendritic arborization followed by dendritic pruning, and synaptogenesis.<sup>32</sup>

At least in the primate brain, the various cortical motor regions are interconnected in complex patterns. For example, the primary motor cortex hand area is interconnected with each of the premotor (or secondary motor) cortex hand areas (PMv, PMd, SMA, cingulate motor areas), as well as parietal areas in the somatosensory cortex.<sup>33</sup> Thus, after injury to M1, a large number of cortical areas are deprived of intracortical connections, and the terminals of many of their constituent neurons lie in ischemic territories. The fate of these corticocortical neurons that have lost their targets was examined in a series of recent experiments in our laboratory.<sup>34</sup> In adult squirrel monkeys, the electrophysiologically characterized M1 hand area was destroyed via electrocoagulation of surface vessels. Then the monkeys survived for 5 months without any type of post-infarct rehabilitative

training. Earlier studies showed that this procedure results in an enlarged PMv hand territory.<sup>35</sup> When the PMv intracortical connections were examined using standard post-mortem tract-tracing techniques, it was found that virtually all the connections were similar to those of control animals in terms of the proportion of labeled terminals or cell bodies found in the connected territories. However, in the somatosensory cortex, a cluster of terminals and cell bodies was found that did not exist in control animals. Specifically, these connections were located in the neuroanatomically and neurophysiologically identified somatosensory area 1/2, a subregion within S1 (FIG. 3). It should be noted that area 1 and 2 are notoriously difficult to differentiate in many non-human primates, and thus, it is not known at this time whether this cluster is in areas 1, or both areas 1 and 2.

This new projection pathway resulting from the ischemic infarct is a true qualitative change. The proportion of PMv connections with S1 increased from about 1% to about 6% of terminals and 12% of cell bodies. In absolute terms, this does not seem like a large number. However, bear in mind that this represents a similar proportion as that between the PMv and PMd, one of PMv's moderate connections in normal animals.<sup>36</sup>

What might be the significance of this new pathway? One hypothesis is that it represents a repair strategy of the sensorimotor cortex to re-engage the motor areas with somatosensory areas. In intact brains, M1 receives input from various regions of the parietal lobe that supply cutaneous and proprioceptive information that is



**FIG. 3.** Rewiring of intracortical connections after focal injury to primary motor cortex. Five months after an ischemic infarct in the hand area of primary motor cortex (M1), connections have formed between the hand area of ventral premotor cortex (PMv) and the somatosensory hand area 1-2.<sup>34</sup>

largely segregated in the M1 hand area—cutaneous information arriving in the posterior portion of M1, and proprioceptive information arriving in the more anterior portion. The functional importance of this somatosensory input can be appreciated from studies employing discrete lesions in these subregions in M1. Lesions in the posterior M1 hand area result in behavioral deficits akin to those seen after S1 lesions. These deficits appear to be similar to sensory agnosia, in which the animal reaches for food items, but does not appear to know whether the item is actually in the hand. In contrast, anterior M1 hand area lesions result in deficits in metrics of the reach, perhaps indicating the disruption of proprioceptive information in the motor cortex.<sup>37</sup> One lesson from these studies is that the motor cortex cannot be considered solely as a motor structure. Deficits result from sensory-motor disconnection in addition to disruption of motor output. Thus, after M1 injury, there is a substantial reduction of somatosensory input to motor areas. Perhaps, the novel connection between PMv and S1 is an attempt by the cortical motor systems to reconnect with somatosensory input.

However, it is not yet known if this connection is functional, or if it is, whether it is adaptive or maladaptive. An alternate hypothesis is that the new pathway represents an aberrant connection that interferes with behavioral recovery. Additional studies are needed to determine the functional consequences of blocking or enhancing this pathway.

### MODULATING NEUROPLASTICITY AFTER STROKE

The significance of neuroplasticity for rehabilitation is that it provides a mechanistic rationale for understanding therapeutic interventions. Thus, it may be possible to develop more effective recovery protocols if we can

elucidate the effects of such interventions on physiological and anatomical plasticity in the injured brain.

As demonstrated by the mapping studies after micro-infarcts in non-human primates noted above, it is clear that behavior is one of the most powerful modulators of post-injury recovery. Behavioral interventions to enhance recovery after stroke have become increasingly popular due to the success of therapeutic interventions such as constraint-induced movement therapy (see also Dromerick, this issue).<sup>38</sup> Whether such behaviorally driven changes in motor performance are due to re-establishment of original motor programs in spared tissue, or due to compensatory use of unimpaired body parts remains a controversial subject.<sup>39</sup> Nonetheless, plastic changes must take place in the spared neuronal substrate whether the improvement is due to true restoration of function or compensation.

Behavioral use clearly plays a role in the contralesional changes that take place in the uninjured cortex of rats following cortical infarction. It has been demonstrated that much of the neuroanatomical plasticity is the result of compensatory reliance on the unimpaired limb. If rats are prevented from using the less impaired forelimb during the first 15 days after injury, the contralesional dendritic growth is prevented.<sup>40</sup> The dendritic growth results from a combination of the effects of the lesion and the compensatory use, as the same results can be obtained after callosal section and compensatory reliance on one limb.<sup>41</sup> Forced use of the limb or callosal transection alone result in only subtle changes in dendrites.<sup>42</sup> Similar conclusions can be reached regarding contralesional synaptogenesis.<sup>43</sup> Other studies have demonstrated that task-specific rehabilitative training is most effective in driving post-injury neuroanatomical changes.<sup>44</sup> Thus, it would appear that CNS injury produces an environment in which the neuronal network is

particularly receptive to modulation by specific behavioral manipulations.

Post-injury use may not be adaptive in all circumstances however. If rats are placed in a vest to force overuse of the impaired forelimb after the injury, the size of the lesion can be increased.<sup>45</sup> This destructive phenomenon, presumably associated with glutamate excitotoxicity,<sup>46</sup> seems to occur only during the first week post-infarct, and only with extreme overuse of the impaired limb.

### ADJUVANT THERAPIES AND THEIR ROLE IN NEUROREHABILITATION

One promising pharmacological approach now being evaluated in clinical trials is the coupling of d-amphetamine (d-AMPH) and rehabilitative training (see also Goldstein, this volume).<sup>47</sup> While d-AMPH has multiple effects in the nervous system, it is thought to exert its influence on recovery mechanisms via noradrenergic pathways. Early animal studies by Feeney and colleagues demonstrated that d-AMPH interacted with training paradigms, improving recovery well beyond that seen with training alone.<sup>48</sup> Small clinical trials were promising, and this approach is now being examined in randomized multi-site clinical trials.

However, recent clinical studies on the use of d-AMPH as a pharmacological adjunct to post-stroke rehabilitation have yielded mixed results as not all participants in these studies benefit.<sup>49,50</sup> To understand the differential factors influencing who benefits from this therapy, a more basic understanding of how d-AMPH influences the central nervous system (CNS) after stroke is needed. An initial step is to address the consequences of d-AMPH upon recovery from ischemic cortical damage in nonhuman primates since they metabolize amphetamines similarly to humans and have similar cortical pre-motor areas that may be involved in recovery of hand function.

We recently examined the effects of a minimal exposure to d-AMPH (a single injection) on recovery of hand dexterity after a cortical infarct in squirrel monkeys. If a single injection is effective, it will be possible to examine the precise time course of neurophysiological and neuroanatomical changes in this nonhuman primate model. Each monkey was randomly assigned to one of three groups: 1) a spontaneous recovery group (SR); 2) a motor skill training group that received a single dose of saline on the first day of training (Sal/Training); and 3) a motor skill training group that received a single dose of d-AMPH (0.25 mg/kg i.m.) on the first day of training (d-AMPH/Training).

Each monkey received a complete infarct to the distal hand area in M1, then an ischemic infarct was made by cauterizing surface vasculature within the defined hand

area. One week following the infarct, all monkeys were impaired on the Klüver board task. A clear, movable Plexiglas barrier was attached to the Klüver board, forcing the monkeys to use their most affected hand, contralateral to the infarct. Post-infarct training on the Klüver board task (1 hour/day) facilitated recovery over 14 days of training by reducing the number of flexions/retrieval necessary to obtain a food pellet. A single injection of d-AMPH given on the first day of training further facilitated improvement in the ability of the monkeys to retrieve food pellets compared with the saline injected monkeys. A follow-up analysis demonstrated that nine weeks after training, the d-AMPH/Training group, but not the Sal/Training group was significantly improved compared with the SR group.<sup>51</sup>

Similar results have recently been shown in rodent models, but with higher doses given at multiple time points during training. Adkins and Jones demonstrated that d-AMPH facilitated recovery of motor skills on a reach and retrieval task for rats using multiple doses of 1 mg/kg, i.p. of d-AMPH.<sup>52</sup> Two and three months after post-infarct training, improvement in reaching skills was not maintained relative to saline-treated rats with the same post-infarct training. The enhanced rate of recovery facilitated by d-AMPH was subsequently demonstrated in a similar rat model using 2 mg/kg d-AMPH by Gilmore and associates.<sup>53</sup> These results seem to be consistent with previous noradrenergic explanations of how amphetamine facilitates recovery of function in that it may cause a release from diasthesis or enhance neural transmission within affected motor systems as well as promoting anatomical changes that can maintain improvements long after the drug has been eliminated.

Another adjuvant therapy that has shown promise in both animal studies and early phase clinical trials is the use of direct, low-level electrical stimulation of the peri-infarct cortex following stroke in motor cortex.<sup>54,55</sup> While the mechanisms by which electrical stimulation affects the behavioral induction of recovery is not well known. Animal studies have demonstrated changes in functional maps induced by stimulation+training, and stimulation appears to induce dendritic growth in a frequency specific manner.<sup>55-57</sup>

### SUMMARY

It is now clear that CNS injury induces widespread neuroanatomical and neurophysiological changes in spared tissue. The uninjured tissue may be particularly receptive to modulation by various exogenous means including behavioral training, plasticity enhancing drugs, and electrical stimulation. Significantly more work needs to be done to understand the mechanisms underlying post-injury plasticity, but recent results from animal models suggest that it may be possible to create an adap-

tive environment in spared neuronal tissue for promoting maximal post-injury recovery.

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