Postinfarct Cortical Plasticity and Behavioral Recovery

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Abstract—Plasticity phenomena in the cerebral cortex after ischemic injury have been documented repeatedly over the past 2 decades both in animal models and in human stroke survivors. This review highlights many of the major neuroanatomic and neurophysiological changes that characterize poststroke plasticity in experimental animals. Spared regions adjacent to the infarct and far removed from the infarct undergo functional alterations that are modified by behavioral experience. Recent evidence is also reviewed, demonstrating that long-range intracortical pathways can be rerouted to completely novel territories. The implications of this new finding for understanding the brain’s capacity for recovery are discussed. (Stroke. 2007;38[part 2]:840-845.)

Key Words: animal models ■ basic science ■ cortical mapping ■ map cortex ■ neurophysiology ■ physiotherapy ■ plasticity ■ stroke recovery

More than 2 decades of experimentation in the cerebral cortex have demonstrated a large number of examples of the phenomenon called cortical plasticity. Throughout an individual’s life, dendrites and spines branch and proliferate, synapses form and degenerate, and the efficacy of synaptic contacts is modulated within a complex network of intracortical connections. Thus, it is not surprising that after an injury to the cerebral cortex, the structure and function of sensory and motor regions are drastically altered. Postinjury plasticity has not only been documented at the molecular, synaptic, cellular, network, and systems levels in experimental animals, but many of these events have been correlated with alterations in cortical function with the use of various neuroimaging and stimulation techniques in humans. At this point in the development of the field of postinjury plasticity, we are still at a decidedly phenomenological stage. With few exceptions, we have been able to document plastic phenomena with great precision and reliability but have not provided conclusions regarding necessity or sufficiency in behavioral recovery. In fact, it has been difficult to determine whether such phenomena are adaptive or maladaptive. Nevertheless, the field has progressed substantially since the mid-1980s, when it was discovered that after peripheral nerve injury, the deprived somatosensory cortex is not silent but instead becomes responsive to inputs from adjoining skin fields.

Although these plastic phenomena are triggered by many endogenous and exogenous events, it is now clear that one of the most potent modulators of cortical structure and function is behavioral experience. Emergent properties of each cortical area are constantly shaped by behavioral demands, driven largely by repetition and temporal coincidence. For example, skilled motor activities requiring precise temporal coordination of muscles and joints must be practiced many times over. Such repetition drives motor cortical areas to form discrete modules in which the conjoint activity is represented as a unit rather than fractionated and individual muscle contractions. Somatosensory discrimination training is characterized by expansions in the representations of stimulated skin surfaces and reductions in receptive field size of individual cortical neurons.

Injury to the motor cortex results in a potent disruption of these coordinated networks and the underlying emergent properties, resulting in loss of fine motor control and the employment of compensatory movement strategies. It now appears that such a disruption to the cortical motor network triggers a major reassembly of interareal and intra-areal cortical networks. Postinjury behavioral experience appears to be critical to the reassembly of adaptive modules. More recent data, collected in nonhuman primates after focal cortical injuries, seem to suggest that the basic intracortical wiring plan that associates information not only among the multiple motor areas but between frontal motor areas and parietal somatosensory areas is substantially altered. This new information provides both a challenge and an opportunity to understand the brain’s inherent mechanisms for functional recovery after stroke.

Translational Value of Stroke Models in Animals

From the outset, it must be noted that current animal models do not mimic clinical stroke per se. Clinical stroke is often a consequence of several predisposing conditions such as cardiovascular disease and related obesity, diabetes, high blood pressure, and age. Animal models have been designed to produce an experimental ischemic insult to cortical and/or subcortical structures typically in otherwise healthy, young to middle-aged animals.

To understand neural mechanisms of cell death and survival, as well as neuronal plasticity after ischemic injury, it is necessary to control confounding covariates. Of course, this is the primary advantage of modeling focal ischemia in animal
models. Age, experience, diet, phenotypic characteristics, and even genotypic characteristics can be precisely controlled. Thus, although we would hope that results of such studies would translate to the clinical condition of stroke, it must be understood that these are models of ischemic injury, not the complex clinical conditions that result in stroke.

**Unique Properties of Primate Brains**

The advantages and disadvantages of using nonhuman primates to model functional recovery after stroke have been discussed at length in other venues.\(^9,10\) The failure of clinical trials for neuroprotection with the use of glutamate antagonists contributed to considerable controversy, including discussions regarding the choice of rodent species.\(^11\) The need for demonstration of safety and efficacy in nonhuman primates has been emphasized in several consensus reports such as the Stroke Therapy Academic Industry Roundtable in 1999.\(^12\) However, it is important to avoid gross generalizations based on superficial similarities and differences among species. On the basis of cost and ethical considerations alone, it is not feasible to use nonhuman primates indiscriminately in studies of neurological disorders. We must carefully consider the goals of the particular experiment and base the use of nonhuman primates on the unique properties of the system under study and the extent to which these properties relate to experimental outcomes. Most of the species differences that will be considered are anatomic distinctions because these differences can be assessed most objectively. For a discussion of similarities in motor behaviors in rodents and primates, see the report of Whishaw.\(^13\)

**Brain Size**

In general, brain weight, as well as brain/body weight ratio, is higher in primate species.\(^14\) This distinction may have some importance for the delivery of compounds via intrathecal administration or direct application. If a therapeutic agent relies on diffusion, such as large molecules that cannot cross the blood-brain barrier, obviously brain size and degree of cortical folding will affect penetration and ultimately the locus of effect. However, with regard to size alone, other species, such as carnivores, would suffice just as well. In fact, the cortices of many nonhuman species, such as carnivores, are relatively nonconvoluted and thus would be poor models for understanding penetration in large brains.

**Anatomy of the Corticospinal Tract**

Because the corticospinal tract is the main descending pathway from cerebral cortex to spinal cord motoneurons and its cortical territories and/or fiber tracts are often injured in clinical stroke, it is important to review its comparative anatomy to assess the utility of various species. The corticospinal tract shares many basic traits in all mammalian species. Universally, the corticospinal tract originates from layer V pyramidal cells in the cerebral cortex. In all mammals, most corticospinal neurons are located in a large contiguous region of frontoparietal cortex corresponding primarily to primary motor (M1) and primary somatosensory (S1) cortex. In all mammals, corticospinal neurons also originate from a secondary focus corresponding to the parietal opercular areas, primarily from the second somatosensory area (S2). In all mammals, the corticospinal fibers descend through the internal capsule and medullary pyramids. With few exceptions, \(\approx 90\%\) of the corticospinal fibers cross the midline at the medulla-spinal cord junction. Thus, many fundamental traits of the corticospinal tract are shared by all mammalian species, suggesting that this pathway emerged early in mammalian evolution.\(^15\)

However, there are also substantial differences among mammalian species in the anatomy of the tract. The total number of corticospinal neurons is substantially greater in primate species than in rodent species with respect to numbers per unit body weight or brain weight.\(^16\) A larger number of corticospinal fibers at least partially account for a substantially greater volume of white matter in the internal capsule of primates compared with rodents. In all primates, but in no other species, corticospinal neurons originate from a unique cortical location, corresponding to the ventral premotor cortex (PMv). In rodents (and rabbits), corticospinal neurons originate from a different, unique location, corresponding to the rostral forelimb area (RFA).\(^15\) In the spinal cord, the principal corticospinal tract trajectory is via the dorsolateral funiculus in primates but via the dorsal funiculus in rodents.\(^17\) Finally, the general rule in mammals is that corticospinal neurons synapse disynaptically and polysynaptically onto motoneurons. However, many (but not all) primate species possess a subset of corticospinal neurons that synapse monosynthetically onto motoneurons.\(^18\) Such monosynaptic connections do not exist in rodents.

**Differentiation of Somatosensory and Motor Areas in Primates**

Because the middle cerebral artery is frequently affected in clinical stroke, it is important to consider differences in the frontal and parietal territories that this artery supplies. In all mammalian species, including all rodents and primates, at least 2 somatosensory representations, S1 and S2, have been identified in the parietal cortex (Figure 1). However, in primates, S1 can be subdivided into additional areas, including areas 3a, 3b, 1, and 2.\(^19\) In rodents, 2 motor areas have been identified, the caudal forelimb area (CFA) and the RFA.\(^20\) In primates, frontal cortex has been subdivided into \(>5\) regions including M1, supplementary motor area (SMA), PMv, dorsal premotor cortex (PMd), and cingulate motor areas.\(^21\) Each of these areas has been further subdivided into subfields (such as SMA proper and pre-SMA).

There has been considerable discussion regarding the relationship of the rodent RFA and various primate motor areas. Although this discussion is beyond the scope of the present article, it should be noted that whereas RFA shares some anatomic features with SMA and some with premotor cortex, it is likely that RFA evolved independently in rodents, and its functional significance cannot be compared directly with that of primate motor areas.\(^20,22\)

Thus, the primate sensorimotor cortex is characterized by a substantial differentiation of primordial regions into separate subareas. After focal injury, functional specialization in these subareas may result in unique functional deficits in primate species compared with rodents or other species.
Intracortical Connectivity of Sensorimotor Areas

Another property that is directly related to the differentiation of sensorimotor areas is that each of these separate subfields has a specific subset of intracortical connections with other areas. Rodents and primates are similar with respect to local, intrinsic intracortical connections, such as the network of local connections within M1 of primates or CFA of rodents.23 Likewise, both rodents and primates possess long-distance intracortical connections between somatosensory areas in the parietal cortex and the main motor forelimb area. In addition, CFA and RFA are interconnected in rodents, as are the various motor areas of primates.20,24–26 Thus, rodents may be reasonable models for understanding alterations in intracortical communication after injury. However, with the diversity of sensory and motor areas in primates, the complexity of intracortical connectivity is qualitatively different. Thus, to fully understand the disruption and potential plasticity of network interactions among motor areas after stroke, it will be necessary to evaluate nonhuman primate species.

In summary, rodents remain valuable resources for understanding plasticity mechanisms after injury. Even a sample size of 8 or 10 animals per group that might be required in a rodent study is typically not feasible in primates. The decision to use nonhuman primates in such studies must be based on unique attributes of primate anatomy and behavior. These unique attributes may in some circumstances dictate whether nonhuman primates should be used in preclinical trials when therapeutic interventions have been developed solely in rodent models.

Functional Plasticity in Cortical Motor Maps After Injury

A decade ago, we demonstrated that local changes occur within the functional representations of the hand in M1 after a subtotal ischemic injury.27,28 Neurons in the adjacent, intact tissue within the M1 hand area survive. In fact, in the particular bed occlusion infarct technique that we used, the penumbra, or region of vulnerable neurons, is very narrow. However, in the absence of postinjury rehabilitative training, the spared hand area is reduced in size, giving way to expanding proximal representations. In contrast, when monkeys underwent rehabilitative training, the hand area was preserved. Presumably, the training, which encouraged increased use and reacquisition of skill in the impaired hand, affected the local network interactions within the spared cortex, maintaining the efficacy of those neurons projecting to hand motoneurons.

However, as described above, primate brains are endowed with a rich intracortical network that allows reciprocal communication among the various sensory and motor areas. Thus, in more recent work, we have examined the effects of M1 infarcts on other motor areas. PMv was a logical location for these initial investigations primarily for the following reasons: (1) The PMv hand area is conveniently located within a few millimeters rostral and lateral to the M1 hand area and thus can be explored electrophysiologically in the same surgical procedure. (2) One of the main intracortical inputs to the M1 hand area is the PMv hand area. Thus, one would expect substantial alterations in its function after focal injury in M1.

Because studies on the time sequence of events in PMv after M1 injury are still in progress, the complete picture remains sketchy. In this report we summarize the results to date. A few days after ischemic injury to the entire M1 hand area, there is no frank neuronal loss in PMv,29 suggesting that these neurons survive destruction of their intracortical targets and partial deafferentation (attributable to destruction of reciprocal intracortical connections from M1). At this time, neurons in the PMv hand area (as well as in the infarct and peri-infarct zone) express vascular endothelial growth factor (VEGF) protein.29 Similar results have been shown in the infarct and peri-infarct regions of rodents, but this study represents the first examination of remote motor areas connected with the site of injury in a nonhuman primate species. VEGF may have at least 2 roles: First, it is well known for its endothelial growth factor properties, and thus upregulation of VEGF may be involved in early stages of angiogenesis. At this early stage after injury, VEGF may also...
play a neuroprotective role. Thus, the upregulation of VEGF in PMv neurons may be attributable to ischemia in the targets of these neurons. However, we do not yet know whether the neurons that express VEGF are the same ones that project to M1.

In rodents, it is well known that the excitability of remote areas is altered for significant periods of time after injury. N-Methyl-D-aspartate (NMDA) receptors are upregulated, whereas γ-aminobutyric acidA (GABAA) receptors are downregulated in both the ipsilesional and contralesional hemispheres. In our squirrel monkey M1 injury model, we recently replicated these results. Seven days after M1 injury, NMDA receptors are upregulated and GABAA receptors are downregulated. These effects appear to be specific to regions interconnected with the injured zone.

Motor maps of the hand in PMv undergo a nonlinear change in motor representational area after M1 injury. Early after M1 injury (2 to 3 weeks), PMv maps invariably shrink. The increased excitability in this region does not result in a simple expansion of motor maps at this time point. It is possible that this early change in excitability disrupts the local intracortical network. In contrast, 3 to 5 months after M1 injury, even in the absence of postinfarct rehabilitation (ie, spontaneous recovery), the PMv maps often are expanded. The state of NMDA receptors and GABAA receptors at this time is unknown.

Expansion of hand representations in PMv in the chronic state (3 to 5 months) after M1 injury is linearly dependent on the size of the M1 injury. Lesions <≈50% of the M1 hand area result in chronic reductions in PMv hand area; lesions >50% result in expansions of PMv hand area. Complete M1 hand area lesions result in an increase of ≈50% in the PMv hand area. Furthermore, the specific locus of subtotal lesions in M1 does not appear to be a significant factor in PMv hand area changes. That is, small, subtotal lesions in the rostrolateral portion of the M1 hand area (M1r) result in the same magnitude of change in PMv maps (ie, small reductions) as small, subtotal lesions in the caudolateral portion of the M1 hand area (M1c). This is important because PMv projections to the M1 hand area are not homogeneously distributed. The vast majority of these fibers terminate in M1r, whereas relatively few fibers terminate in M1c. One might hypothesize that small lesions in the M1c hand area would result in greater changes in PMv because such a lesion results in greater disruption of the corticocortical network. However, lesions in both locations result in similar reductions in PMv hand area when examined in the chronic state.

This intriguing result harks back to the principle of mass action espoused by Lashley in the 1920s. Lashley stated that “efficiency of performance is conditioned by the quantity of nervous tissue available and is independent of any particular area or association tract” and “for some problems, a retardation results from injury to any part of the cortex, and for equal amounts of destruction the retardation is approximately the same. The magnitude of the injury is important; the locus is not.”

Lashley’s mass action principle has often been disputed because it is too simplistic and seems to discount the distinct functional specialization of cortical areas. However, if one considers Lashley’s statements with regard to a specific cortical region (such as the M1 hand area) rather than to the entire cortex, it seems wholly consistent with our data. The M1 hand area has often been referred to as a shared neural substrate for control of the hand. Dense local intracortical networks interconnect neurons across the entire hand area. The divergence and convergence of corticospinal neurons from the M1 hand area to motoneuron pools in the spinal cord result in a structure that is not entirely homogeneous but cannot be considered a “labeled line” either. Thus, small lesions in the M1 hand area may result in similar changes in remote structures regardless of the degree of connectivity with that structure. With small injuries, the remaining M1 hand area may have enough remaining capacity that expansion (ie, “vicariation”) in the remote premotor area is not necessary.

**Alteration of Intracortical Connectivity After Focal Cortical Lesions**

Because the principal target of PMv intracortical fibers is destroyed by an M1 hand area lesion, the fate of these fibers is certainly of interest in understanding the organization of the surviving network. Previous studies have demonstrated that axonal sprouting occurs in the peri-infarct tissue of adult animals, as demonstrated in the barrel cortex of rats. Peripheral nerve injury is also known to induce intracortical sprouting within somatosensory cortex. Local axonal sprouting has also been demonstrated in visual cortex after retinal injuries. In addition, cortical efferent fibers are alterable in adults after injury. For example, corticostriatal fibers, which are primarily ipsilateral, sprout from the intact, contralesional cortex and terminate in the contralateral striatum on the side of the lesion.

Such plasticity in crossed descending fiber systems may provide one mechanism for the remaining intact hemisphere to participate in recovery.

However, relatively little is known regarding the changes in intracortical networks after focal injury. In a recent series of experiments led by Dancause, we examined the intracortical connections of the PMv hand area after an M1 hand area injury. To allow sufficient time for any potential anatomic reorganization to occur, we tracked squirrel monkeys for 5 months after the injury. Then the neuroanatomic tracer biotinylated dextran amine was injected into the PMv hand area, and sufficient time was allowed for transport to the terminals of PMv fibers within the cortex (as well as neuronal somata that project to PMv, although we will only discuss PMv efferents in the present review). In quantitative examinations of the terminal fields of PMv, intracortical fibers were largely unchanged in each of the cortical areas examined except one. Each animal that had sustained an injury to the M1 hand area displayed a remarkably consistent, dense cluster of PMv terminal boutons within the somatosensory cortex. Specifically, these terminals were located in area 1 to 2 immediately caudal to the physiologically and anatomically identified 3b hand area, i.e., in the area 1 to 2 hand representation (note that areas 1 and 2 are notoriously difficult to differentiate in many nonhuman primate species). In normal monkeys, PMv terminal boutons in area 1 to 2 account for only ≈0.5% of all intracortical terminals originating from PMv. However, after the injury to M1, PMv terminal boutons in area 1 to 2 accounted for 6% of PMv intracortical terminals. Although 6% may not seem like a large proportion, consider that in the normal brain, this is equivalent to the proportion of connec-
tions between PMv and PMd (6%) or between PMv and SMA (8%), intracortical connections that we consider "moderate." This study by Dancause et al represents the first evidence of a major alteration of intracortical wiring patterns between different cortical fields (in fact, different cortical lobes) in any adult mammal (Figure 2).

What might be the functional significance of such a drastic alteration in cortical connectivity? In addition to the major connection between M1 and PMv that is lost after M1 lesions, other intracortical pathways are also disrupted. M1 normally receives substantial input from somatosensory cortex, conveying proprioceptive and cutaneous information that is presumably integrated with motor output commands in M1. These somatosensory inputs terminate in M1 in a segregated fashion, with proprioceptive inputs primarily in the rostral portion of the M1 hand area and cutaneous inputs in the caudal portion. Subtotal lesions of the rostral versus caudal sectors of the M1 hand area result in dissociable deficits related to the nature of the somatosensory inputs. Thus, lesions in M1 do more than disrupt motor output pathways via corticofugal tracts. Such lesions effectively disconnect motor cortex from the somatosensory system. It is possible that the establishment of new connections between PMv and S1 provides a means by which the remaining cortical motor system can gain access to somatosensory signals. It remains for future experiments to determine the validity of this hypothesis. At this point it is equally likely that these aberrant connections represent a maladaptive alteration that potentially interferes with motor recovery.

Regardless of the functional significance of this finding, it is now clear that we can no longer consider the injured brain as a normally wired brain with a missing puzzle piece. In this study, we focused only on the PMv. However, other intracortical pathways are also connected with M1 and presumably also undergo some degree of rewiring. Thus, at least after focal injuries to the cortex, the surviving brain tissue may be substantially altered in its basic anatomic connectivity. This result provides both challenges and opportunities. The challenges are many, as we will now need to understand the rules governing reconnectivity after focal injury, if there are predictable rules to discover. But this result also provides many opportunities to use exogenous interventions (drugs, behavior, stimulation) in an attempt to modulate postinjury adaptation.
anatomy in a more adaptive way. This surprising ability of the cerebral cortex may yield important clues to improving functional recovery in stroke survivors.

Sources of Funding
This work was funded by National Institutes of Health grant RO1 NS030853.

Disclosures
None.

References
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Stroke. 2007;38:840-845
doi: 10.1161/01.STR.0000247943.12887.d2
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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