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Motor System Reorganization After Stroke: Stimulating and Training Toward Perfection

Stoke instigates regenerative responses that reorganize connectivity patterns among surviving neurons. The new connectivity patterns can be suboptimal for behavioral function. This review summarizes current knowledge on post-stroke motor system reorganization and emerging strategies for shaping it with manipulations of behavior and cortical activity to improve functional outcome.

As of 2010, there were more than 33 million stroke survivors worldwide, a population that is predicted to rise to 70 million by 2030 (63). The disability burden of stroke now falls most heavily on those between 20 and 75 years of age (110). Hemiparesis of the upper extremity (hand and arm) is the most prevalent (114), and among the most enduring and disabling (76), consequences of stroke, interfering with life quality and productivity. Despite thousands of promising preclinical studies of neuroprotective treatments that minimize tissue damage from stroke, their effective translation to clinical stroke populations has been disappointing (42, 147). Thrombolytic treatments to restore blood flow during the acute phase of stroke can be very effective in reducing impairments (166), but due to a short (3–4.5 h) treatment window and risk of hemorrhage, few stroke patients receive them (1, 62). Thus, as it stands now, the options for minimizing stroke-induced brain damage are limited, and the need to better understand and better treat the functional aftermath of this damage continues.

There is usually some degree of spontaneous improvement in function after stroke. Two general mechanisms are thought to contribute to this. 1) There is a resolution of temporary disruptions in neural activity, metabolism, and blood flow in regions connected to and surrounding the injured tissue. 2) Surviving neurons reorganize their connectivity patterns in a manner that supports partial restoration of, or compensatory substitution for, the lost functions. These are interrelated mechanisms (FIGURE 1). Despite them, most stroke survivors are left with chronic disability.

Neural reorganization after stroke is initiated by cellular reactions to degeneration. As neurons in an ischemic region die, their axons and synapses degenerate in widespread brain regions, instigating regenerative responses that promote the growth of new connections among surviving neurons. There is tremendous potential for variability in the patterns, and functional benefit, of the new connectivity that emerges from this process.

Several factors influence neural reorganization patterns, as reviewed below. A major one of these is the activity of the neuronal populations contributing to new connections. The intrinsic malleability of neural connections to altered neural activity underlies the capacity to learn across the lifespan. By influencing neural activity patterns, behavioral experiences drive the growth, maturation, and selective survival of synapses in relevant circuits. After stroke, behavioral experiences that influence the activity of regenerating circuits can potentially shape neural reorganization patterns (90).

This creates an opportunity to use manipulations of behavior and neural activity to shape brain reorganization in a manner that optimizes functional outcome. There has been a surge of excitement in recent years over the potential to do this, as reflected in major growth in the field of stroke neurorehabilitation. However, the question of how best to do it is far from answered. More detailed understanding of what constitutes optimal neural reorganization after any given stroke, its behavioral dependencies, and other conditionalities are needed, but rapid advances in the field support optimism that this is within reach, given sufficient attention.

Below, we review recent research on neural reorganization after stroke, with a focus on motor system reorganization and its contribution to upper extremity function. Behavioral interventions such as motor rehabilitative training can shape neural reorganization to improve function. However, self-taught compensatory behavioral strategies can be a dominant force in driving reorganization patterns and can do so in a manner that interferes with motor rehabilitative training efficacy. Rehabilitative training alone is usually insufficient to restore normal function, but it has the potential to be improved by its combination with other treatments. We highlight one promising...
strategy for this: that of combing behavioral training with cortical stimulation.

**Regenerative Responses to Stroke**

Ischemic stroke is characterized by a gradient of reduced blood flow, with a core of severely reduced blood flow and severe tissue damage, and a surrounding penumbra, where blood flow reduction and degenerative reactions are less extreme (79). The loss of blood supply initiates a cascade of metabolic failure, excitotoxicity, mitochondrial breakdown, oxidative stress, and neuroinflammation that, if not quickly reversed, results in irreparable tissue damage (57). As neurons die in the ischemic region, connected regions undergo axonal degeneration, synapse loss, glia reactivity, and neuronal dysfunction or death to varying degrees, depending on the original connectivity with the ischemic region (15, 57, 81).

Degeneration triggers regenerative counter-reactions that can be observed on molecular to network levels, as reviewed in detail elsewhere (91, 135, 143). Briefly, degeneration elevates molecules that promote cell survival and proliferation and the structural remodeling of dendrites, axons, and synapses (157, 198). Growth inhibitory molecules that normally limit axonal plasticity in the adult brain are reduced (33, 130), and surviving neurons sprout new axon collaterals to reinnervate neurons in the penumbra and other denervated regions (17, 155). New synapses tend to be produced exuberantly followed by selective synapse pruning and maturation (174). Axonal sprouting and synaptogenesis are coordinated with dendritic remodeling in postsynaptic (2, 41, 187) and presynaptic (7, 152) neurons. The neuronal growth responses are intercoordinated with glial, vascular (10, 80), and extracellular matrix remodeling (157, 171). The whole process yields a system with new connectivity patterns, sometimes with much altered excitatory and inhibitory activity patterns (34, 96, 193).

Although regenerative responses to injury appear to be an intrinsic capacity of the adult central nervous system (CNS), they have many conditionals and constraints. In adult CNS, axonal reinnervation is mainly accomplished by collateral sprouting of remaining projections within, or proximal to, the denervated region rather than long-distance growth of new axons (50, 51). For example, reinnervation of dentate gyrus granule cells after perforant path lesions is accomplished mainly by sprouting from remaining fibers terminating in the same layer (71). Nevertheless, even

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**FIGURE 1.** Mechanisms of spontaneous functional improvements after stroke

A: coronal section illustrations of some of the axonal projections of cortical pyramidal neurons. Death of neurons in the core of an ischemic infarct results in denervation and disrupted activity in afferent targets, the striatum and contralateral cortex in this example. In peri-infarct cortex, there is a gradient of blood flow reductions, denervation of intracortical connections (not shown), and various degrees of dendritic retraction in surrounding neurons. Over time, blood flow and metabolic activity are restored, and denervated regions are reinnervated by axonal sprouting and synaptogenesis, resulting in reorganized connectivity. Restoration and reorganization are interrelated, e.g., reinnervation may depend on some degree of blood flow recovery and contribute to its fuller restoration. B: illustration of potential changes in neural connectivity patterns after reinnervation. The relative quantities of synapses from the contralateral vs. ipsilateral cortex may substantially change. Other sources of synaptic input to these neuronal populations can contribute to reinnervation and alter the balance of excitatory and inhibitory activity.
collateral sprouting can profoundly alter connectivity patterns (48). The more abundant and more active remaining afferents tend to contribute most to reinnervation (25, 32, 35, 69, 159, 165). This makes neural activity a promising therapeutic target, as discussed below. Axonal degeneration is a major trigger for remaining axons to sprout (44, 175), a relatively local signal, such that sprouting and accompanying dendritic remodeling patterns can be expected to vary tightly with degeneration patterns, which of course varies with injury territories. Regenerative plasticity also varies with injury modality; regenerative responses to ablation and traumatic brain injury are more limited compared with ischemic injury (95, 183, 186). There are numerous other contributors to variable regenerative responses, including injury severity (103), age (137, 156), individual genetic differences (154), and common stroke comorbidities, such as diabetes (80, 176).

Motor System Reorganization After Stroke

Hemiparesis is a prevalent consequence of stroke due to its tendency to involve the vascular supply of cerebral motor regions and their projection pathways, e.g., territories supplied by branches of the middle cerebral artery. Strokes are often positioned to disconnect cortex from its output to midbrain, brain stem, and spinal cord as a result of subcortical damage to descending fiber tracts, direct damage to motor cortex, or a combination of the two. As a result, axons carrying motor commands from motor cortex to subcortical targets, including spinal cord, are lost. Descending axons from surviving cortical neurons sprout to reinnervate these subcortical targets.

Most animal studies of subcortical reinnervation have examined projections arising from the uninjured (contralesional) primary motor cortex (M1), which after cortical infarcts or middle cerebral artery occlusions can sprout midline-crossing fibers that reinnervate striatum (35, 129), red nucleus, and spinal cord (113, 115, 121, 151, 191). The focus on sprouting from contrallesional cortex reflects, in part, the ease in detecting it in the quantity of fibers crossing at midline. However, surviving neurons of the ipsilesional cortex can contribute as well. Starkey et al. (173) found that, after infarcts of the M1 forelimb region in rats, corticospinal projections from the hindlimb region, which normally terminate in lower spinal cord levels, reinnervate the cervical spinal cord (upper limb region). Liu et al. (121) found that both hemispheres contribute to spinal cord reinnervation after middle cerebral artery occlusion in mice. It is likely that projections from the contralesional cortex necessarily predominate after injuries that spare little of the ipsilesional pathways (20) (FIGURE 2).

It seems reasonable to think that the capacity of the new subcortical connections to mediate the return of movement varies with the neuronal populations that supply them, but this has yet to be conclusively determined. There is strong evidence that sprouting from either hemisphere contributes to improved function, as supported by correlations and gain- and loss-of-function manipulations (e.g., Refs. 115, 151, 173, 188). However, Liu et al.’s study mentioned above found that final behavioral improvements were correlated with the contribution of ipsi- but not contralesional cortex to subcortical reinnervation. There is also suspicion that, when contralesional projections dominate reinnervation, it contributes to the development of abnormal muscle synergies in the paretic limb (128).

Direct damage to M1 results in extensive dendritic remodeling of remaining cortical neurons and reorganization of their connectivity. The dendrites and spines of pyramidal neurons near a cortical infarct partially degenerate followed by varying degrees of regrowth over time (22, 40, 109). In adult rats, M1 infarcts lead to sprouting of new intracortical axons that travel from the ipsilesional rostral motor cortex (analogous to primate premotor cortex) to synapse in the peri-infarct M1 (17, 32, 119). Similarly, after infarcts of the M1 hand representation in monkeys, axons from the ipsiversal premotor cortex sprout into peri-infarct M1 and somatosensory cortex (48). Transcallosal projections from the contralesional motor cortex also contribute to reinnervation of peri-infarct cortex (32, 36, 121).

Axonal sprouting and synaptogenesis create new patterns of synaptic connectivity, which can be expected to alter neural activity patterns (e.g., Refs. 31, 61). On a larger scale, neural reorganization is reflected in the organization of cortical maps of body movements (movement representations) and skin surfaces (somatosensory representations), and in cortical activation patterns related to movement and sensation (17, 45, 46, 75, 143). In animal and clinical studies, paretic limb function has been strongly linked to the reorganization of movement (68, 144, 148, 167, 181) and somatosensory (23, 43) cortical representations in the injured hemisphere and with the return to more normal patterns of activity across motor regions (75, 101, 141, 161). That the sprouting of new axonal connections contributes to at least some of these changes is suggested by close spatial relationships between regions of somatosensory (43) and motor (48) cortical map reorganization, and regions providing and receiving new projections.
There is bilateral neuroanatomical reorganization of motor cortex after unilateral motor system injury (91, 169). Unilateral damage to M1 results in degeneration of transcallosal cortical projections, which instigates dendritic remodeling of layer V pyramidal neurons of the contralateral cortex in rats (87, 88, 92). If the injuries sufficiently impair one forelimb, leading to compensatory reliance on the other (nonparetic) forelimb, this promotes a major increase in dendrites and synapses in layer V of the contralateral cortex (2, 27, 94). Pyramidal neurons in contralateral M1 that contribute to subcortical reinnervation also grow more dendrites after middle cerebral artery occlusions in rats (152). In both rodents and humans, the contralateral motor cortex has increased excitability (170, 193), increased fMRI activation during stimulation or movement of the paretic side (54, 75), and reduced functional connectivity (interdependent activity patterns) with the injured hemisphere (101, 161), effects that vary with stroke locus and severity and may contribute to paretic limb impairments (30, 72, 122, 172, 190).

At present, there is still a piecemeal understanding of how these various facets of neuroanatomical reorganization unfold over time, but there is every indication that, while the process takes a long time overall (months at least), it is particularly dynamic earlier after injury (33, 75, 81, 82, 135, 161, 164). Thus it can be predicted that there is both a protracted time period for modulating the reorganization process therapeutically and a time-sensitivity in the potency of this modulation (10).

Many elements of motor system reorganization are sensitive to manipulations of behavioral experience and neural activity. For example, electrical stimulation of contralateral cortex increases sprouting of contralateral corticospinal projections (25, 31). Sprouting of intracortical axons is increased by forced use of the paretic forelimb (149). Compensation with the nonparetic limb promotes dendritic growth in the contralateral cortex (94). Motor map reorganization is enhanced by training the paretic forelimb, as described below. Glial and vascular remodeling responses also are highly sensitive to behavioral manipulations (reviewed in Refs. 10, 89).

Motor system reorganization is also linked with changes in behavioral function, although not always to improvements. As noted above, the reorganization of motor (145) and somatosensory maps (43), intracortical sprouting (150), synaptogenesis in peri-infarct cortex (3), and corticospinal

![FIGURE 2](http://physiologyonline.physiology.org/) Neuroanatomical reorganization after stroke

A: illustration of a rat brain sectioned coronally near the rostral edge of the M1 forelimb representation region (green). Callosal, corticorubral, and corticospinal tract projections of forelimb M1 are illustrated in an intact brain. B: after subtotal infarcts of the forelimb area, remaining neurons of the forelimb region and surrounding motor cortex of the injured hemisphere can contribute to reinnervation. C: larger infarcts can severely damage descending projection pathways or the cortical pyramidal neurons that give rise to them, leaving crossed collaterals of contralateral projections as a primary source of reinnervation. The rubrospinal neuron illustration shows potential alterations in relative quantities of synaptic input from ipsi- and contralateral M1.
sprouting from either hemisphere (115, 121, 173) are positively correlated with functional improvements. However, the contralesional dendritic growth in layer V pyramidal neurons that we have observed has no known benefit (83), and contralesional M1 activity can have disruptive influences on paretic limb function (47, 126, 134, 141). Sprouting can also be maladaptive. For example, sprouting of proprioceptive afferents from the muscles into denervated spinal cord contributes to hyperreflexia (177), and sprouting in the hippocampus contributes to seizure susceptibility (59). Thus neural reorganization after stroke can be beneficial, irrelevant, suboptimal, or maladaptive for functional outcome. This leads to the need to drive these responses in beneficial directions. Their sensitivity to behavioral experience and neural activity provide obvious tools for this purpose.

Wrangling Behavioral Experience to Optimize Motor System Reorganization

The Trouble With Compensation

The natural response to disability is to learn new ways of accomplishing daily activities, i.e., to develop compensatory behaviors. Stroke survivors with upper extremity impairments typically learn to rely on the nonparetic hand and arm for daily activities. This encourages disuse of the paretic side, known as “learned-nonuse,” which has long been believed to exacerbate impairments (179). Our studies in rodent models indicate that learning new skills with the nonparetic side also can subvert neural mechanisms of functional improvements in the paretic forelimb.

We have modeled the effects of compensatory skill learning with the nonparetic forelimb in rodents using skilled reaching tasks that require movements resembling those used by humans (192) and permit control over lateralization and quantity of experience (8, 97). Following unilateral ischemic M1 lesions, if rats or mice receive a period of daily training with the nonparetic limb training (NPT) on a novel (for the limb) reaching task, disuse and dysfunction of the paretic forelimb is exacerbated (8, 9, 11, 98), regardless of whether the reaching skill is entirely novel to either limb (11) or had been established in the paretic limb before the infarct (8). In contrast, training one limb of intact rats has no detrimental effect on the other limb. MacLellan et al. (124) found that the deleterious effects of NPT persist long after the training ceases. The functional improvements that can be achieved with subsequent rehabilitative reach training focused on the paretic forelimb are also lessened (8, 9, 98), although prior NPT does not diminish activity with the paretic forelimb during rehabilitation.

The effect of NPT on rehabilitation efficacy is linked with reduced neuronal activation (8) and loss of forelimb movement representations (104) in peri-lesion M1 (FIGURE 3), a region known to mediate functional improvements in the paretic limb, as explained below. Animals that receive rehabilitative training after NPT have a greater increase in synaptic densities in the residual forelimb region compared with rehabilitative training alone (104). That is, NPT does not block neural reorganization of peri-infarct cortex but rather alters it in a manner that is maladaptive for the paretic forelimb. The promotion of synapse addition in peri-infarct cortex by NPT may interfere with subsequent synaptic changes that can be driven by rehabilitative training.

Together, these results suggest that, at least after direct M1 damage, learning to rely on the nonparetic side can interfere with the capacity of peri-infarct cortex to change in a manner that benefits paretic limb function. This is problematic given that such compensation tends to develop quickly after stroke and is a dominant strategy for dealing with impairments. However, it appears to be specifically deleterious to learn new unimanual skills with the nonparetic side while disusing the paretic forelimb. Impairments in the paretic limb are not exacerbated if both limbs are trained in an alternating fashion (8) or if NPT is paired with greater skilled bimanual activity in the home cage (98). Thus it is possible that the deleterious effects of compensating with the nonparetic side could be minimized with sufficient involvement of the paretic side in skilled unimanual or bimanual activity.

Transcallosal projections of the contralesional M1 are involved in the deleterious effects of NPT on paretic forelimb function (9). If callosal fibers are severed or the contralesional M1 is damaged before the onset of NPT, it has no deleterious effect on the paretic limb. The involvement of interhemispheric connections in NPT effects makes it seem likely the compensation with the nonparetic limb contributes to the clinical observations of abnormal interhemispheric activity and disruptive influences of contralesional M1 on paretic limb movement (134, 141). It also raises the possibility that NPT effects would vary depending on the severity of stroke-induced damage to transcallosal projection territory, a possibility that we have not yet fully tested.

That the contralesional M1 mediates the deleterious effects of NPT hardly precludes it from making beneficial contributions to paretic limb function. There are ample suggestions in the literature that contralesional cortex can contribute to
functional improvements in the paretic limb, e.g., in reinnervating spinal cord (115, 151, 188). In addition to its effects on peri-infarct cortex, NPT promotes dendritic and synaptic growth in the contralesional M1 (2, 26, 123), but these effects do not appear to be directly responsible for the maladaptive effects of NPT. Callosal transections do not block the promotion of contralesional dendritic growth by NPT, but they do block its deleterious effects on paretic limb function (9).

Behavioral training that improves function in the paretic limb can also increase dendritic growth (18) and synaptogenesis (93) in contralesional M1. Nevertheless, it is quite possible that the contralesional dendritic growth resulting from NPT is coupled with changes in the axonal projections from the same region that are maladaptive. For example, NPT might drive greater transcallosal connectivity in peri-infarct cortex that competes with intracortical reinnervation, e.g., from premotor cortex. As noted above, after larger infarcts, the contralesional hemisphere is likely to be a predominant source of new neural connections in denervation regions. It may matter most that these new connections are driven by behavioral experience to subserve functional improvements in the paretic rather than exclusively the nonparetic forelimb.

While it is not feasible to replicate our rodent behavioral manipulations in a similarly controlled fashion in humans, our findings are highly consistent with behavioral and neural phenomena of learned-nonuse suggested by Taub et al. (178, 179). Since experience with the weakness and ineptitude of the paretic side leads to reliance on the nonparetic limb, this reduces practice with the paretic limb, reducing its influence on neural reorganization. Once this compensatory pattern is well established and, as our findings suggest, its influence on neural reorganization is established, behavioral interventions probably need to work harder to counteract it.

The clinical rehabilitation approach, Constraint-Induced Movement Therapy (CIMT), was developed to counter learned-nonuse (133). This involves constraining the nonparetic limb for most waking hours during a period of intense motor rehabilitative training of the paretic limb. Clinical trials strongly support the efficacy of CIMT for improving motor function after stroke (111, 112, 194). Our finding that NPT promotes synapse addition in peri-infarct cortex (104) suggests another potential mechanism for CIMT efficacy, one based on synaptic competition. Synapses that more effectively activate a postsynaptic neuron are selectively maintained and matured at the expense of less active ones (12, 78). It may be that constraining the nonparetic limb reduces activity at synapses that were created in response to learning to compensate with this limb. In the converging neural circuitry of the two limbs (e.g., peri-infarct motor cortex), this would be expected to facilitate the formation, maturation, and survival of synapses activated by experiences of the paretic limb. That is, CIMT could be effective, in part, because it
confers a competitive edge at the synaptic level to experiences of the paretic, over the nonparetic, limb.

**Motor Rehabilitation**

It is now well established that practicing motor skills with the paretic upper extremity enhances behaviorally relevant neural reorganization after stroke in both humans (28, 56, 86, 120, 168) and animal models (18, 93, 145). For example, the improvements in upper limb motor function resulting from CIMT are associated with enlargement of the motor map of the hand in M1 (120, 168). In animals with subtotal lesions of the forelimb region of M1, training the paretic forelimb in skilled reaching tasks after resuscitates, maintains, and reorganizes movement representations in the remaining forelimb territory of M1 (37, 145, 160). Without rehabilitative training, forelimb movement representations near the infarct are lost (104, 144). Disrupting motor cortical reorganization prevents the training-induced functional gains (160). Rehabilitative training also reduces the size of movement representations of the nonparetic forelimb in contralesional M1 (13).

While motor map reorganization is strongly correlated with functional improvements, it is delayed relative to these improvements (144). Thus it is better said to reflect, rather than explain, the mechanisms of functional improvement. It is nevertheless a very useful neural correlate because it bridges findings from animal and clinical studies. In intact animals, motor skill training instigates in motor cortex time-dependent changes in gene expression, protein synthesis, synaptic potentiation, and synapse addition, which is localized to regions of motor map reorganization (4, 108). After M1 infarcts, there is close correspondence between cortical map reorganization and axonal sprouting patterns (43, 48), and rehabilitative training also increases synaptic densities and synapse maturation in forelimb movement representations (3, 104). Thus it may be that the reorganization of movement representations in peri-infarct cortex reflects that substantial underlying changes in cortical connectivity have already occurred.

Rehabilitative training effects vary with training intensity (16), age (181), and timing (10, 196). In animal studies, rehabilitative training initiated within the first weeks after CNS injury results in greater functional gains and more profound neural changes than does later training (14, 19, 153). Early skill practice with the paretic limb also counteracts maladaptive NPT effects (98). Clinical studies also support that earlier behavioral interventions are more effective than later ones (122, 162). For example, Lang et. al (112) found that constraint-induced movement therapy (CIMT) is more effective for improving motor performance when initiated 3–9 mo post-stroke compared with later onsets. These findings are consistent with the idea that earlier interventions can interact with more dynamic phases of neural remodeling to promote better reorganization. However, there is also potential for early interventions to worsen impairments (58, 195). There is a need for a more detailed understanding of the neural bases of time-sensitivities in rehabilitation efficacy (10).

One possibility is that early, but not too early, interventions are most effective in shaping neural reorganization. Lee et al. (116) found that axonal sprouting from contralesional M1 in rats is increased by reach training initiated at 5 days, but not 1 or 14 days, after cortical infarcts, potentially reflecting that there are optimal stages of axonal reinnervation to target. Consistent with this, Wahl et al. (188) found that motor rehabilitative training in rats with cortical infarcts could be improved by combined treatment with an antibody (Nogo-A) that promotes corticospinal tract sprouting, but only if the antibody treatment preceded the training rather than being administered concurrently. The sequential treatment resulted in a more orderly pattern of spinal cord reinnervation, suggesting that its superior efficacy could be a result of the rehabilitative training being timed to stabilize and refine the new connections of sprouting axons.

Although the knowledge needed to wield them is incomplete, we consider behavioral manipulations to be a core tool set for promoting functionally useful neural reorganization after stroke. They rely on the intrinsic brain mechanisms for gaining new functionality, the experience-dependent neural plasticity underlying learning (106). At present, rehabilitation strategies are often far from sufficient to normalize function. There has been a growing focus on strategies for enhancing rehabilitation efficacy by combining it with neural plasticity-facilitating treatments.

**Modulating Cortical Activity to Improve Function**

**Epidural Cortical Stimulation**

In rats and monkeys, combining training of the paretic forelimb on skilled reaching tasks with concurrent high-frequency (50–100 Hz) cortical stimulation (CS) delivered via epidural or subdural electrodes over peri-infarct M1 enhances performance improvements compared with training alone (5, 6, 38, 107, 132, 158, 182, 199). In most studies, CS was delivered at 50% of movement thresholds continuously during reach training. The performance improvements were linked with increases in dendritic and synaptic densities (3, 5,
findings seem to imply that the efficacy of CS for posttreatment compared with controls. These maintained functional improvements out to 24 wk in this participant subset (118). In addition, a analyses, significant improvements were found evoked movements in the hand. In follow-up study, only 16% of subjects had stimulation-and 42% of subjects, respectively. In the and 42% of subjects, respectively. In the earlier clinical studies and the possibility that the earlier treatments influence neural reorganization in a manner that cannot be accomplished later. The findings that CS promotes corticofugal sprouting (31), dendritic plasticity (6, 200), and synaptogenesis (3) are generally consistent with this possibility. However, it also remains possible that the timing dependency could be overcome with different stimulation frequencies, different current intensities, or more robust behavioral training.

Injury severity is a major variable in the efficacy of epidural CS. CS is less effective in improving rehabilitation efficacy in rats with more severe behavioral impairment levels (3), and effective stimulation parameters vary between small and large infarcts (132). Findings from clinical trials are consistent with the possibility that CS efficacy varies with injury severity. While two early clinical studies (phase I and II trials) of epidural CS combined with motor practice supported its safety and efficacy to improve motor function (24, 117), a larger phase III trial failed to demonstrate its efficacy 4 wk posttreatment when all participants were included (118). The main difference between the animal and earlier clinical studies and the phase III trial was in the proportion of participants in which hand movements could be evoked by CS. In the phase I and II studies, movements were evoked in 100% and 42% of subjects, respectively. In the phase III study, only 16% of subjects had stimulation-evoked movements in the hand. In follow-up analyses, significant improvements were found in this participant subset (118). In addition, a greater proportion of the entire CS cohort maintained functional improvements out to 24 wk posttreatment compared with controls. These findings seem to imply that the efficacy of CS for increasing functional gains, but not for promoting the persistence of these gains, depends strongly on a minimum level of integrity in descending corticospinal pathways.

Transcranial Cortical Stimulation

The non-invasive stimulation approaches of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have emerging potential for improving motor function after stroke. In healthy humans, transcranial stimulation over motor cortex modulates cortical excitability to improve motor speed and accuracy (49, 185), general hand function (21), and motor learning (29, 139, 162, 180). There is now a major effort to determine the post-stroke therapeutic potential of these stimulation approaches.

Repetitive TMS (rTMS) uses 5- to 20-Hz pulse trains to facilitate neural activation or ~0.2- to 1-Hz trains to inhibit neural activation, referred to as high- and low-frequency rTMS, respectively. rTMS over motor cortex increases motor-evoked potential amplitudes in acute stroke (53), reduces spasticity and hemiparesis in chronic stroke subjects (125), and improves grasping function after subcortical stroke (142). The size of TMS coils makes it challenging to deliver during rehabilitation regimens, but it alters cortical excitation for a period after stimulation to facilitate learning “off-line” (39, 65, 84).

tDCS uses relatively weak electric currents (~1–2 mA) that modulate neural activity via effects on ion channel activation (64, 65, 140). Excitatory tDCS (anodal) enhances motor learning, likely by strengthening synaptic connections through NMDA receptor-dependent long-term potentiation (LTP)-like effects (70, 131, 138). After stroke, excitatory tDCS delivered over the affected motor cortex or inhibitory tDCS delivered over the contralesional motor cortex improves motor performance on standardized tests of motor function (66, 84, 85, 102).

Many transcranial stimulation studies have focused on restoring the balance of interhemispheric activity after stroke, based on findings of increased excitability of the contralesional hemisphere, which may overly inhibit activity in the injured hemisphere (30, 55, 77, 170, 193). Animal studies also support an increase in GABAergic activity in peri-lesion cortex (34, 197). It follows that balancing interhemispheric activity, either by exciting the injured hemisphere or by inhibiting the contralesional cortex, might improve function. Consistent with this, facilitatory stimulation (high-frequency TMS or anodal tDCS) over the stroke-affected motor cortex or disruptive stimulation (low-frequency TMS or cathodal
tDCS) can acutely improve performance of the paretic side (52, 66, 67, 84, 85, 99, 100, 105, 127). However, the influence of excitability in the contralesional cortex, and hence the efficacy of disruptive stimulation in this hemisphere, is likely to vary with stroke subtypes (e.g., cortical vs. subcortical) (30, 72, 75). The efficacy of stimulating either hemisphere may vary with timing, stimulation parameters, impairment severity, and integrity of ipsilesional M1 (64).

Many of the effects described above were only evident for a short period of time after stimulation, but more enduring motor improvements result from stimulation coupled with motor training (105, 136, 184, 189). For example, tDCS paired with 10 consecutive occupation therapy sessions improved paretic upper limb function compared with therapy alone for up to 6 mo, as assessed with the Fugl-Meyer Score (102). Vestito et al. (184) found that tDCS paired with practice in naming in aphasic patients improved naming performance for 16 wk compared with controls. There are emerging applications for transcranial stimulation in combination with robot-assisted training (60, 74) and brain-machine interfaces (73).

There are clearly many details to work out to optimize and tailor parameters of transcranial stimulation for treating stroke disability (64, 163). Nevertheless, these studies together with those of epidural CS converge to support that extrinsic modulation of cortical activity can be used to improve the short- and long-term functional gains from rehabilitation.

Conclusions and Future Perspectives

Motor system stroke instigates a dramatic and widespread reorganization of the connectivity of surviving neurons, involving extensive axonal sprouting, dendritic remodeling, and synapse formation in either hemisphere. This is linked with reorganization of motor and sensory cortical maps, and bilateral changes in neural activity and functional connectivity patterns. Some, but hardly all, of these changes are functionally beneficial.

The current excitement over the potential to drive optimal reorganization with behavioral manipulations and neural activity modulators is well founded, but the neural focus of the efforts could stand to be much better informed. Much of our understanding about the functional relevance of motor system reorganization is based on correlations between brain and behavioral change. In the context of the dramatic remodeling response instigated by stroke, the potential to mistakenly infer causality from coincidence is high. The behavioral relevance of reorganization involving the contralesional motor cortex is especially murky. Excitability changes in contralesional cortex are sometimes, but not always, linked with worsened function. Dendritic growth and synaptogenesis in contralesional cortex is increased by manipulations that improve paretic limb function and by those that worsen it. We think that the devil is likely to be found in the details: for neural changes in either hemisphere to subserve functional improvements in the paretic upper limb requires the right input, in the form of experiences of the paretic limb, at the right time.

It is probably typical for experiences of the nonparetic forelimb to be a dominant force in driving post-stroke brain reorganization, because the compensatory reliance on this limb involves major new skill learning, which is heavily practiced, the sort of experience that is very effective at promoting plasticity even in intact brains. At least after M1 injury, this learning counteracts the capacity to remodel the injured hemisphere to better subserve function of the paretic limb. The job of improving paretic limb function via motor rehabilitative training may become all the more challenging as a result. Earlier onsets of rehabilitative treatments may be more effective not only because they interact with early dynamic phases of neural remodeling but also because they rein in maladaptive effects of compensating with the nonparetic side.

Even with early onset rehabilitation, there is still much room for improvement. Although the process of optimizing and tailoring them is ongoing, cortical stimulation approaches are showing major promise for their potential to do this. There are many hints that cortical stimulation efficacy can vary with post-stroke timing, injury locus, and injury severity. The efforts to tailor and optimize these approaches would benefit from a clearer distinction between the neural remodeling events in either hemisphere that are adaptive, maladaptive, and irrelevant for paretic limb function and how they vary after different strokes.

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References


10. Allred RP, Kim SY, Jones TA. Use it and/or lose it: experience effects on brain remodeling across time after stroke. Front Hum Neurosci 8: 379, 2014.


104. Kim SY, Allred RP, Adkins DL, Tennant KA, Don-

105. Kim YH, You SH, Ko MH, Park JW, Lee KH, Jang SH, Kim YO, Kim BK. Repetitive transcranial magnetic stimulation-induced corticotor ex-

106. Kleim JA, Jones TA. Principles of experience-
dependent neural plasticity: implications for re-

lation enhancing upper extremity task perfor-


113. Liu Z, Zhang RL, Li Y, Cui Y, Chopp M. Remodel-
ing of the corticospinal innervation and sponta-

114. Lotz M, Beutling W, Loibl M, Domin M, Platz T, Schumine K, Byblow WD. Contralateral motor cortex activation depends on ipsilesional cortico-
spinal tract integrity in well-recovered subcorti-

115. Luke LM, Allred RP, Jones TA. Unilateral ischemic sensorimotor cortical damage induces contral-
lesional synaptogenesis and enhances skilled re-


117. Mally J, Dinya E. Recovery of motor disability and spasticity in post-stroke after repetitive trans-


119. Mansur CG, Fregni F, Boggio PS, Bertolino M, Gallucci-Neto J, Santos CM, Wagner T, Rigonatti SP, Marcolin MA, Pascual-Leone A. A sham stim-

120. McMorland AJ, Runnalls KD, Byblow WD. A neu-
roanatomical framework for upper limb syn-

121. McNeill TH, Brown SA, Hogg E, Cheng HW, Me-

122. Mironova YA, Grefkes C, Ameli M, Fink GR. Inter-
network interactions in the human motor cortex by repeated non-invasive brain stimula-


125. Nudo RJ, Mil liken GW. Reorganization of move-


127. Overman JJ, Carmichael ST. Plasticity in the in-
jured brain: more than molecules matter. Neuro-


130. Papadopoulos CM, Tsai SY, Cheatwood J, Boll-
now MR, Kolb BE, Schwab ME, Kajtzebl GW. Den-
drictic plasticity in the adult rat following middle cerebral artery occlusion and Nogo-a neutraliza-

Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. Neurorehabil Neural Repair 22: 505–513, 2008.


5143, 2012.

