Remodeling the Brain With Behavioral Experience
After Stroke

Theresa A. Jones, PhD; Rachel P. Allred, BA, BS; DeAnna L. Adkins, PhD; J. Edward Hsu, MD, PhD;
Amber O’Bryant, BA; Mónica A. Maldonado, BS

Background and Purpose—Behavioral experience can drive brain plasticity, but we lack sufficient knowledge to optimize
its therapeutic use after stroke.

Methods—We outline recent findings from rodent models of cortical stroke of how experiences interact with postinjury
events to influence synaptic connectivity and functional outcome. We focus on upper extremity function.

Results—After unilateral cortical infarcts, behavioral experiences shape neuronal structure and activity in both
hemispheres. Experiences that matter include interventions such as skill training and constraint-like therapy as well as
unguided behaviors such as learned nonuse and behavioral compensation. Lateralized behaviors have bihemispheric
influences. Ischemic injury can alter the sensitivity of remaining neocortical neurons to behavioral change and this can
have positive and negative functional effects.

Conclusions—Because experience is ongoing in stroke survivors, a better understanding of its interaction with brain
reorganization is needed so that it can be manipulated to improve function and prevent its worsening. (Stroke. 2009;
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Key Words: learned nonuse ■ motor cortex ■ motor rehabilitation ■ synaptic plasticity

Behavioral experience can cause dendrites to grow and
regress, synapses to change in efficacy, vasculature and
glia to be modified, and, sometimes, neurons to be added or
lost.1 It is at work continuously and across the lifespan. It is
safe to assume that it will be a factor in stroke recovery.
However, what pragmatic use can we make of this? Current-
ly, experience, in the form of physical therapy and
rehabilitation, is the major tool available for treatment in the
chronic poststroke period, but we lack the knowledge re-
quired to optimize its use alone or in combination with other
treatments. Animal research is beginning to reveal how
behavioral experience interacts with degenerative and regen-
erative cascades after stroke onset. This research suggests that
the nature and timing of behavioral experiences can have a
major influence on brain reorganization with good, bad, and
mixed consequences for functional outcome.

Shaping Postinjury Experience
Brain damage can impair and enhance experience-dependent
plasticity depending on the region and time window after the
injury.1,2 We have found that, in rats with unilateral ischemic
sensorimotor cortical lesions, the contralesional motor cortex,
in concert with transcallosal degenerative changes, becomes
more sensitive to behavioral experiences of the ipsilesional
“unaffected” forelimb (Figure).3 After these lesions, rats
spontaneously begin to rely more on the unaffected forelimb
and this drives the growth of synapses and dendrites in the
contralesional cortex. More synapses also have ultrastructural
c characteristics of enhanced efficacy. These effects occur
more robustly than those resulting from similar asymmetrical
forelimb experience in intact animals. Thus, this is an
example of injury-induced enhancement of experience-
dependent plasticity.

The facilitation of plasticity in the contralesional cortex
may enhance an animal’s ability to learn compensatory ways
of using the unaffected forelimb. Consistent with this, even in
the presence of significant impairments in the “unaffected”
limb, some types of skill acquisition with this limb are
enhanced, an effect that is lesion size- and time-sensitive.3,4
However, there is a cost for the impaired limb. When rats
were trained to use the unaffected limb for skilled reaching in
the weeks after injury, it reduced neuronal activation (as
assayed by FosB/ΔFosB expression) in the remaining peri-
infarct motor cortex, a region that is important for recovery of
the impaired limb.5 This was linked with slowed recovery of
skilled motor function in the impaired limb and an exacerba-
tion of its disuse.3,5 Thus, experience with the unaffected limb
has bihemispheric neuronal effects that can simultaneously
enhance function in the unaffected limb and worsen function
in the impaired limb.

Humans with cerebral stroke have altered interhemispheric
excitability and abnormal influences of the intact hemisphere

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From the Department of Psychology and Institute for Neuroscience, University of Texas at Austin, Austin, Texas.
Correspondence to Theresa A. Jones, PhD, Seay Hall, 1 University Station A8000, University of Texas at Austin, Austin, TX 78712. E-mail
tj@psy.utexas.edu
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over the stroke-affected hemisphere. Our animal research suggests that experience-dependent plasticity could contribute to unbalanced interhemispheric activity. Attempts to improve impaired limb function, for example using constraint-induced movement therapy, may have to overcome some neuronal changes driven by experience with the unaffected limb. Like with humans, anesthetization of the unaffected limb in rats transiently improves function in the impaired limb. Unfortunately, it can sometimes be detrimental to restrict use of the unaffected limb too intensely early after a stroke. Thus, we need to learn how to safely shape early behavioral experience to prevent it from driving brain plasticity in a suboptimal direction for bilateral function.

**Enhancing Neurorehabilitation**

Behavioral improvements, neuronal structural plasticity, and brain functional changes can be driven by targeted poststroke behavioral rehabilitative therapies in humans and animal models as reviewed previously. For example, targeted training of the impaired upper extremity in motor skills enhances motor map reorganization near cortical infarcts and improves motor function.

A limitation of motor rehabilitative training is that it can take much time and effort to greatly improve function and, even then, it may be far from sufficient to normalize it. It might be enhanced by its combination with therapies that facilitate its neuromatric changes. An approach that we and others have investigated is combining motor training with motor cortical stimulation (CS).

In rats and monkeys with motor cortical ischemic lesions, daily training in skilled reaching results in greater functional improvements when administered concurrently with CS. The CS was delivered epidurally or subdurally in the peri-infarct cortex at levels subthreshold to that needed to evoke movements.
help to activate remaining motor cortical neurons so that they can participate in the synaptic plasticity underlying motor relearning. Consistent with this possibility, CS with motor training increases dendrites and synapses (Figure D), and potentiates motor cortical-evoked potentials. Currently, it is unclear whether the benefits of epidural CS can be reproduced in human stroke survivors. However, a broader implication of these animal studies is that facilitation of training-induced plasticity may greatly improve functional outcome after cortical ischemia.

**Conclusion**
Experience is a potent factor in brain restoration and reorganization that can both improve and impair function. A more detailed knowledge of experience–injury interactions is needed to tailor manipulations of experience for time, injuries, and individual characteristics in a manner that optimizes restorative brain plasticity and functional outcome.

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None.

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