

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; 40[suppl 1]:S136-S138.)

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? Currently, 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 required to optimize its use alone or in combination with other treatments. Animal research is beginning to reveal how behavioral experience interacts with degenerative and regenerative 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 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/ Δ FosB expression) in the remaining perinfarct 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 exacerbation 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

Received August 4, 2008; accepted August 8, 2008.

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

© 2009 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.108.533653

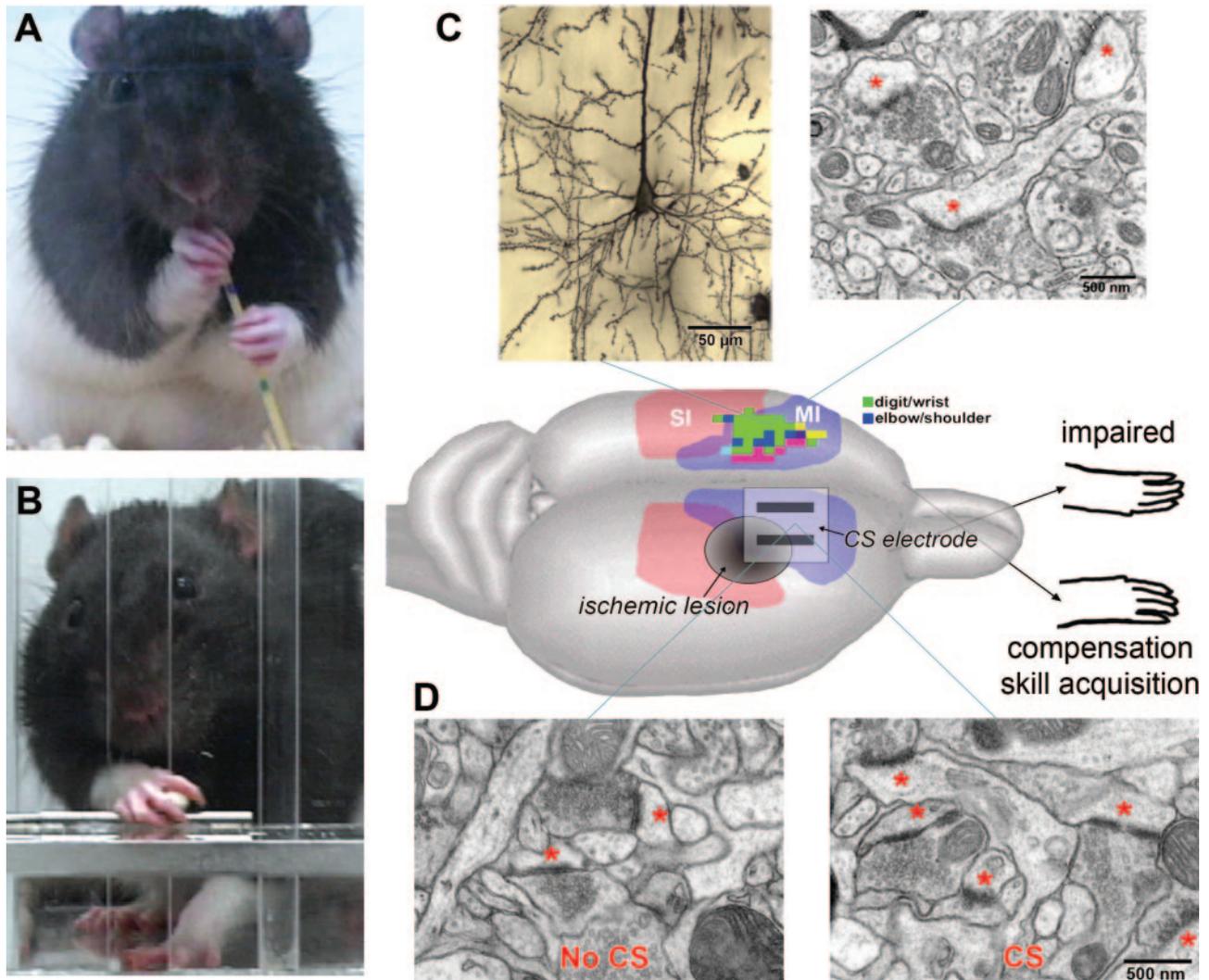


Figure. Behavioral interventions change the course of neural reorganization after sensorimotor cortical infarcts. Rats use their forepaws in dexterous ways for food handling (A) and reaching behaviors (B), making them suitable for modeling aspects of upper extremity impairments.^{14,15} After unilateral cortical infarcts, rats have enduring contralesional impairments in sensitive measures of these behaviors, and they develop a reliance on the “unaffected” ipsilesional forepaw. Skill acquisition with the unaffected forelimb interacts with injury-induced cellular changes to drive a robust plasticity of dendrites and synapses (*) in the contralesional motor cortex (layer V, C).^{3,4} However, it also reduces neuronal activation in the peri-infarct cortex and worsens the efficacy of later motor rehabilitative training focused on the impaired forelimb.^{3,5} CS combined with motor training of the impaired limb improves its efficacy and increases the density of dendrites and synapses in the peri-infarct motor cortex (D).^{10,11} MI, primary motor, SI, primary somatosensory cortex.

over the stroke-affected hemisphere.⁶ 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.⁷ Unfortunately, it can sometimes be detrimental to restrict use of the unaffected limb too intensely early after a stroke.^{2,8} 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.^{2,9,10} For example, targeted training of the impaired upper extremity in motor skills enhances motor map reorganization near cortical infarcts and improves motor function.¹⁰

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 neuroplastic effects. An approach that we and others have investigated is combining motor training with motor cortical stimulation (CS).^{6,11–13} In rats and monkeys with motor cortical ischemic lesions, daily training in skilled reaching results in greater functional improvements when administered concurrently with CS.¹² The CS was delivered epidurally or subdurally in the peri-infarct cortex at levels subthreshold to that needed to evoke movements. CS might

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),¹¹ enlarges motor maps,¹² and potentiates motor cortical-evoked potentials.¹³ 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.

Acknowledgments

We thank Drs S. Cramer and R.J. Nudo for their review of the manuscript.

Sources of Funding

The research overviewed here was supported by the National Institute of Neurological Disorders and Stroke grants RO1 NS056839 and U54 NS048126.

Disclosures

None.

References

1. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech Lang Hear Res*. 2008;51:S225–S239.
2. Kleim JA, Jones TA, Schallert T. Motor enrichment and the induction of plasticity before or after brain injury. *Neurochem Res*. 2003;28:1757–1769.
3. Allred RP, Jones TA. Experience—a double edged sword for restorative neural plasticity after brain damage. *Future Neurology*. 2008;3:189–198.
4. Hsu JE, Jones TA. Contralateral neural plasticity and functional changes in the less-affected forelimb after large and small cortical infarcts in rats. *Exp Neurol*. 2006;201:479–494.
5. Allred RP, Jones TA. Maladaptive effects of learning with the less-affected forelimb after focal cortical infarcts in rats. *Exp Neurol*. 2008;210:172–181.
6. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol*. 2006;5:708–712.
7. O'Bryant A, Bernier B, Jones TA. Abnormalities in skilled reaching movements are improved by peripheral anesthetization of the less-affected forelimb after sensorimotor cortical infarcts in rats. *Behav Brain Res*. 2007;177:298–307.
8. Dromerick AW, Lang CE, Powers WJ, Wagner JM, Sahrman SA, Videen TO, Miller JP, Birkenmeier R, Hahn MG, Wolf SL, Edwards DF. Very early constraint-induced movement therapy (VECTORS): phase II trial results. *Stroke*. 2007;38:465.
9. Cramer SC, Riley JD. Neuroplasticity and brain repair after stroke. *Curr Opin Neurol*. 2008;21:76–82.
10. Nudo RJ. Postinfarct cortical plasticity and behavioral recovery. *Stroke*. 2007;38:840–845.
11. Adkins DL, Hsu JE, Jones TA. Motor cortical stimulation promotes synaptic plasticity and behavioral improvements following sensorimotor cortex lesions. *Exp Neurol*. 2008;212:14–28.
12. Harvey RL, Nudo RJ. Cortical brain stimulation: a potential therapeutic agent for upper limb motor recovery following stroke. *Top Stroke Rehabil*. 2007;14:54–67.
13. Teskey GC, Flynn C, Goertzen CD, Monfils MH, Young NA. Cortical stimulation improves skilled forelimb use following a focal ischemic infarct in the rat. *Neurol Res*. 2003;25:794–800.
14. Allred RP, Adkins DL, Woodlee MT, Husbands LC, Maldonado MA, Kane JR, Schallert T, Jones TA. The vermicelli handling test: a simple quantitative measure of dexterous forepaw function in rats. *J Neurosci Methods*. 2008;170:229–244.
15. Cenci MA, Whishaw IQ, Schallert T. Animal models of neurological deficits: how relevant is the rat? *Nat Rev Neurosci*. 2002;3:574–579.

Remodeling the Brain With Behavioral Experience After Stroke

Theresa A. Jones, Rachel P. Allred, DeAnna L. Adkins, J. Edward Hsu, Amber O'Bryant and
Mónica A. Maldonado

Stroke. 2009;40:S136-S138; originally published online December 8, 2008;
doi: 10.1161/STROKEAHA.108.533653

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
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:

http://stroke.ahajournals.org/content/40/3_suppl_1/S136

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Stroke* is online at:
<http://stroke.ahajournals.org/subscriptions/>