# Displacement of Sensory Maps and Disorganization of Motor Cortex After Targeted Stroke in Mice

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***Background and Purpose***—Recovery from stroke is hypothesized to involve the reorganization of surviving cortical areas. To study the functional organization of sensorimotor cortex at multiple time points before and after stroke, we performed longitudinal light-based motor mapping of transgenic mice expressing light-sensitive channelrhodopsin-2 in layer 5 cortical neurons.

***Methods***—Pulses of light stimulation were targeted to an array of cortical points, whereas evoked forelimb motor activity was recorded using noninvasive motion sensors. Intrinsic optical signal imaging produced maps of the forelimb somatosensory cortex. The resulting motor and sensory maps were repeatedly generated for weeks before and after small (0.2 $mm^3$) photothrombotic infarcts were targeted to forelimb motor or sensory cortex.

***Results***—Infarcts targeted to forelimb sensory or motor areas caused decreased motor output in the infarct area and spatial displacement of sensory and motor maps. Strokes in sensory cortex caused the sensory map to move into motor cortex, which adopted a more diffuse structure. Stroke in motor cortex caused a compensatory increase in peri-infarct motor output, but did not affect the position or excitability of sensory maps.

***Conclusions***—After stroke in motor cortex, decreased motor output from the infarcted area was offset by peri-infarct excitability. Sensory stroke caused a new sensory map to form in motor cortex, which maintained its center position, despite becoming more diffuse. These data suggest that surviving regions of cortex are able to assume functions from stroke-damaged areas, although this may come at the cost of alterations in map structure. **(*Stroke*. 2013;44:2300-2306.)**

**Key Words:** brain mapping ■ cerebral cortex ■ mice ■ motor cortex ■ neuronal plasticity ■ somatosensory cortex



Recovery from stroke depends on the ability of surviving neural circuitry to reorganize and compensate for the loss of damaged regions.[1,2] Cortical regions that are in close proximity to the stroke or are functionally related to the damaged region are well positioned for this type of vicarious function, particularly after small strokes.[3,4] For example, destruction of the mouse forelimb sensory cortex by targeted stroke can cause a new sensory representation to emerge in the territory normally occupied by forelimb motor cortex.[5,6] It remains unclear, however, whether the motor cortex can maintain its primary role in addition to shouldering the computational burden previously carried by the somatosensory cortex. The annexation of motor cortex by new sensory representations may require the underlying circuitry to abandon its original function, causing the motor map to be displaced. This type of maladaptive reorganization has been proposed as a mechanism for the secondary deficits that appear several weeks after stroke in some patients.[7,8]

Cortical reorganization persists for months after stroke,[9] but longitudinal experiments in animal models have been constrained by the limitations of intracortical electric stimulation. We made use of transgenic channelrhodopsin-2 mice[10] that express a light-sensitive cation channel in layer 5 cortical output neurons[11] to perform light-based mapping (LBM) of motor cortex.[12] LBM has the advantages of being faster and less invasive than electrode-based mapping[12] and can be repeatedly combined with intrinsic signal imaging[13] of somatosensory representations in cranial window preparations. Here, we present the first longitudinal study of combined sensory and motor cortical reorganization after strokes targeted to mouse forelimb sensorimotor cortex.

## Materials and Methods

For additional details, please see online-only Data Supplement.

### Animals and Surgery

Animal protocols were approved by the University of British Columbia Animal Care Committee. Channelrhodopsin-2 transgenic mice were implanted with a cranial window over the right sensory-motor cortex and allowed to recover for 2 months before being used in mapping experiments. The majority of cranial windows remained viable for the full extent of the experiment (17 of 24 mice). Each group contained 4 male and 4 female mice (except motor stroke group: 5 males, 3 females). Age at mapping onset was consistent between groups (sensory 148.2±10.5 days,

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motor 139.1±16.9 days, and sham 133.75±11.8 days; $P$=0.72; ANOVA).

## Intrinsic Optical Signal Sensory Mapping

We conducted 20 to 40 imaging trials per experiment, each comprising 15 frames collected over 1.5 s preceding a tactile stimulus delivered to the contralateral forelimb by a piezoelectric device (1 s of 5 ms square pulses at 100 Hz) and 15 frames collected during and after the stimulus. Images were analyzed using an ImageJ plugin described previously[14] to create an image of mean percentage change in 635 nm light reflectance thresholded at 33% of maximal response.

## Light-Based Motor Mapping

LBM methodology has been described in detail.[12,15] Briefly, we targeted a 473-nm laser beam to a grid of cortical sites in semirandom order. Evoked forelimb movement amplitudes were measured using laser range finders. This process was repeated 3 times to obtain a mean value for each pixel of the map.

## Photothrombotic Stroke

To generate photothrombotic strokes, mice were injected with 1% Rose Bengal in phosphate-buffered saline (100 mg/kg IP).[16] A circular region of cortex 1 mm in diameter was illuminated with the arc lamp of an epifluorescence microscope (10 mW green light, 10× objective, numerical aperture=0.3) for 13 minutes. Sham mice were injected with saline only and illumination was targeted to sensory forelimb (sFL).

## Histology

Infarct volumes were calculated using ImageJ by measuring the area of the infarct in all coronal sections where it was visible and multiplying this value by the distance between sections.

## Statistical Analyses

Data were analyzed using Graphpad Prism. The specific tests used are stated alongside all probability values reported.

# Results

## Longitudinal LBM of Sensory and Motor Forelimb Representations

Twenty-four Thy1-channelrhodopsin-2 transgenic mice[10] were implanted with cranial windows that covered sensorimotor cortex of the right hemisphere (5 mm×5 mm, extending 1 mm across the midline and 2.5 mm anterior and posterior from bregma; Figure I in the online-only Data Supplement). Three baseline motor and sensory mapping sessions were performed

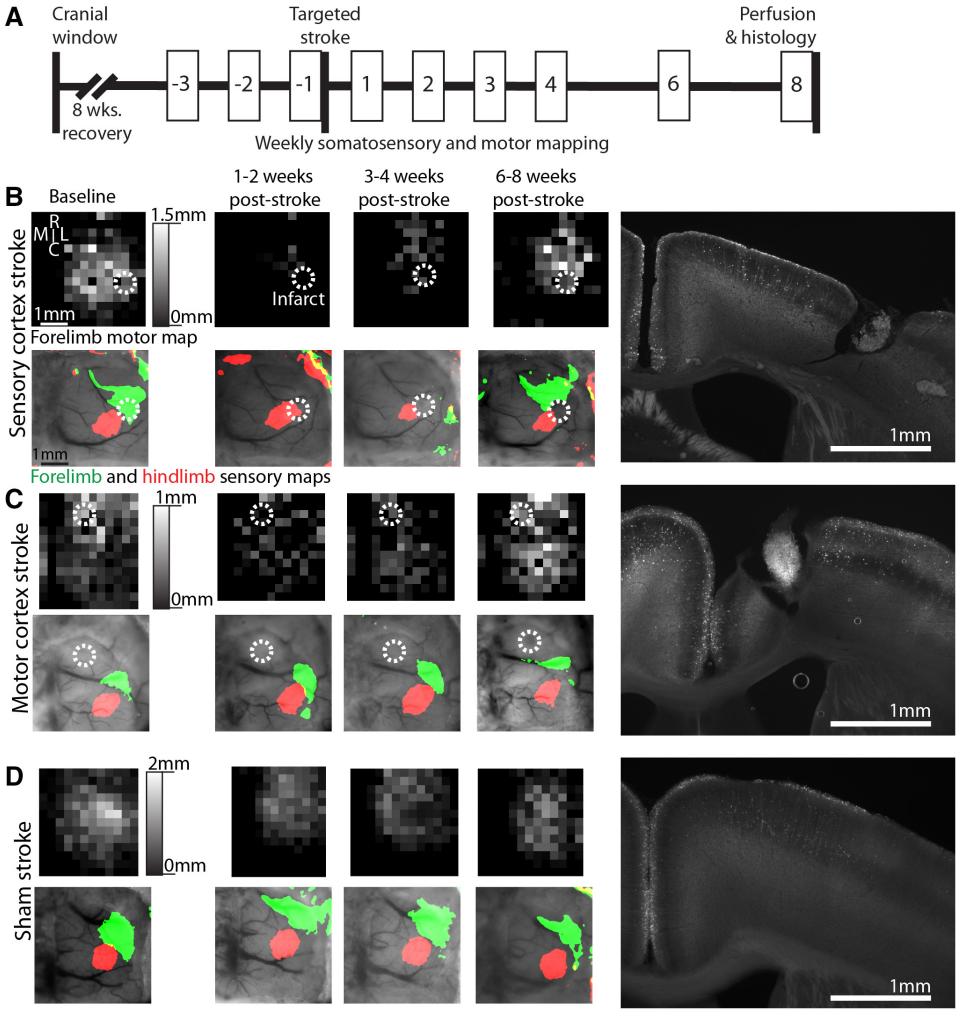


**Figure 1.** Representative examples of sensorimotor reorganization. **A**, Experimental timeline; (**B**) paired forelimb motor (**top**) and somatosensory forelimb and hindlimb (**bottom**) maps from a representative baseline time point (first column), followed by maps from time points after sensory-targeted stroke. All motor maps are the mean of 3 repetitions performed in a single experiment. **Right**, Epifluorescence image of a channelrhodopsin-2-yellow fluorescent protein expressing coronal section with an infarct in somatosensory cortex. **C**, Maps generated before and after a motor-targeted stroke and sham (**D**) stroke. Note that maps represent motor output scaled consistently for each animal, with individual differences in motor excitability reflected between animals.

for each animal (Figure 1A). Contralateral motor forelimb (mFL) maps were spatially stable, with a mean weekly shift in center of gravity of 0.42±0.22 mm (n=24 mice, all values±SEM unless otherwise stated). Contralateral sFL maps exhibited a similar weekly shift in center position during the baseline period (0.42±0.09 mm; n=14 mice).

One day after the third baseline mapping session, a photothrombotic infarct was targeted to either sFL (sensory stroke group; Figure 1B) or a nonoverlapping portion of mFL (motor stroke group; Figure 1C). Infarct volume was comparable for the sensory- and motor-targeted groups (0.18±0.07 versus 0.23±0.06 $mm^3$, respectively; $P$=0.54; $t$ test), with sensory-targeted infarcts located more laterally than motor-targeted infarcts (2.71±0.27 versus 1.87±0.15 mm from midline; $P$=0.0194; $t$ test). No differences were observed in infarct volume between females and males (0.20±0.04 versus 0.23±0.07 $mm^3$; n=6 and 7, respectively; $P$=0.77; $t$ test).

## Spatial Properties of Sensorimotor Reorganization

As in previous studies,[6] strokes targeted to sFL caused the reorganized sFL map to shift medially toward motor cortex (Figure 2A and 2C). Despite its occupation by the new sFL map, mFL was able to maintain its position after sensory stroke (Figure 2B). Similarly, strokes in mFL did not cause a subsequent shift of the neighboring sFL map (Figure 2B and 2C). Sham strokes caused no reorganization of sensorimotor cortex (Figure 2A–2C). Although spatial reorganization was largely confined to the stroke-damaged map, sFL displacement after sensory stroke was correlated with increased mFL displacement (Figure 2D). Displacements of sFL and mFL were not correlated with infarct volume or with the extent of overlap between sensory and motor maps, defined by the prestroke separation between their centers of gravity.

## Changes in Sensorimotor Excitability After Stroke

To assess the responsiveness of the sensorimotor cortex to somatosensory stimuli, intrinsic optical signal values were measured in nonoverlapping regions of interest defined by the baseline positions of sFL and mFL. Vibrotactile stimulation of the contralateral forepaw caused an intrinsic optical signal response in sFL and to a lesser extent in mFL (Figure 3). These sensory responses were unaffected by sham- or motor-targeted strokes (Figure 3). Strokes targeted to sFL, however, caused a persistent deficit in sensory responses within somatosensory cortex (Figure 3, upper left). Responses to sensory stimulation were initially disrupted in mFL, but returned after 6 to 8 weeks.

To examine the effect of targeted stroke on motor representations, each animal's poststroke motor maps were normalized to their own baseline mean, aligned according to the position of the infarct and then averaged. Strokes in mFL caused a decrease in motor output from the infarct core (Figure 4), balanced by a substantial increase in perinfarct motor output not seen after sensory-targeted or sham strokes (Figure 4). Motor output from the immediate vicinity of the stroke was significantly decreased for the first month after both sensory and motor strokes, but recovered by 6 to 8 weeks post stroke (Figure II in the online-only Data Supplement). Normalized map area and motor output after stroke were conserved overall after stroke (Figure III

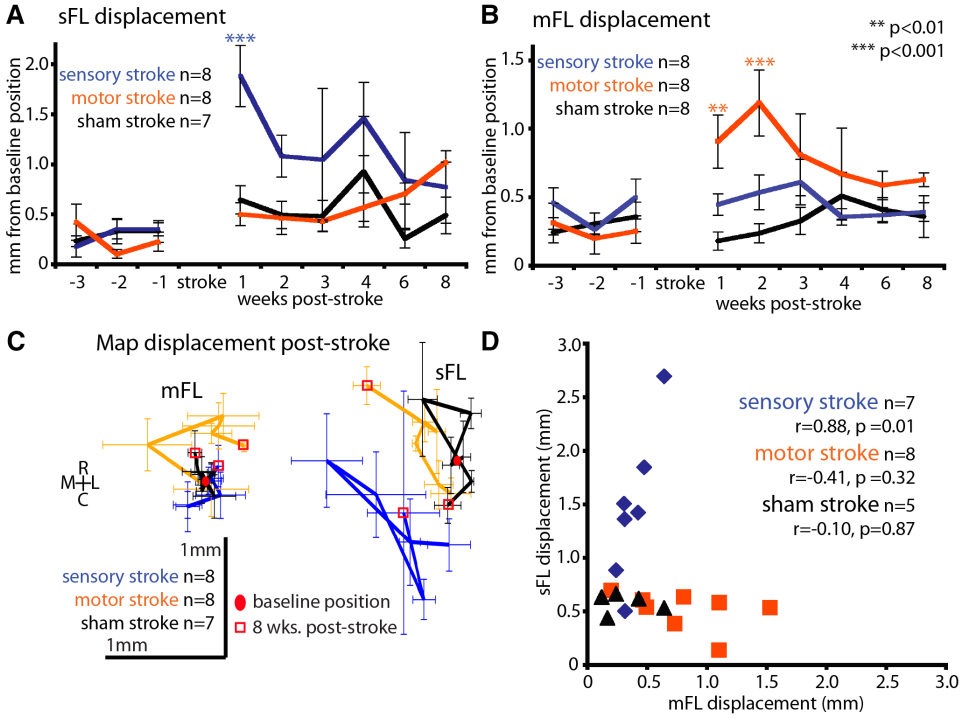


**Figure 2.** Map displacement after stroke. **A**, Displacement of sensory forelimb (sFL) center from its mean baseline position before and after sensory (blue), motor (orange), or sham (black) strokes. Asterisks signify $P$ values (2-way ANOVA; $F(2)$=6.4; $P$=0.002; asterisks correspond to results of Bonferonni's post test). **B**, Motor forelimb (mFL) displacement (2-way ANOVA; $F(2)$=9.572; $P$=0.0002). **C**, Mean weekly position of motor (**left**) and sensory (**right**) forelimb maps relative to their prestroke location. Stroke in motor cortex causes an anterior shift of the mFL map (orange path in **left**), whereas stroke in sensory cortex causes a posteromedial displacement of sFL (blue path in **right**). **D**, Correlation between shifts in sFL and mFL. Error bars in this and all subsequent figures are SEM.

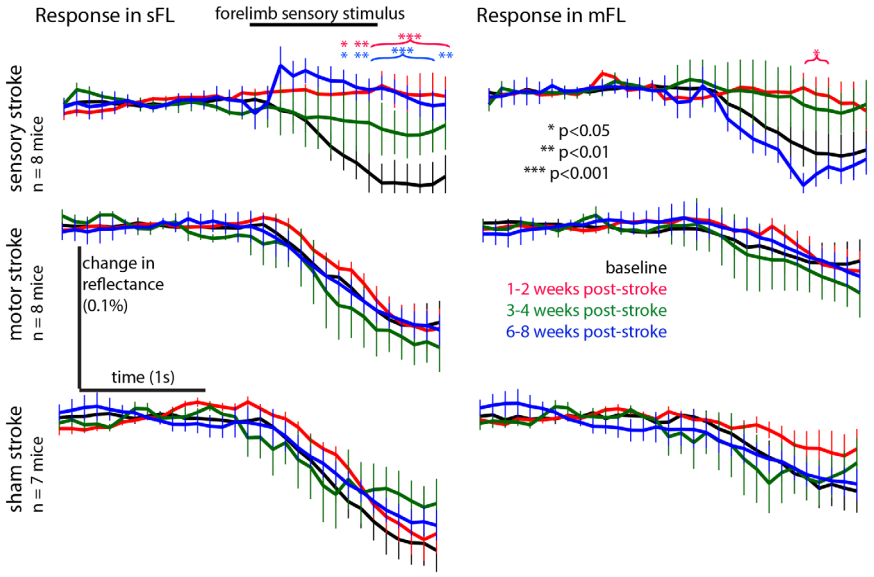


**Figure 3.** Sensory responses after stroke. Each panel contains intrinsic signal responses to stimulation of the contralateral forelimb at time points before and after stroke. Asterisks indicate *P* values from Bonferonni's post test from a 2-way ANOVA of each poststroke time point against the baseline. sFL indicates sensory forelimb; and mFL, motor forelimb.

in the online-only Data Supplement) and were not significantly correlated with infarct volume. No significant sex differences were observed for changes in map area or motor output after stroke.

### Effects of Stroke on the Integrity of Motor Representations

Given the modest size of the infarcts created by targeted photothrombosis, it is perhaps unsurprising that these small strokes did not cause gross changes in motor output or map area. Interestingly, however, we observed that motor maps frequently exhibited an abnormally scattered or diffuse structure after stroke (Figure 1). This effect was particularly pronounced after stroke targeted to sensory cortex (Figure 5A). Because such changes in map structure may not be accurately reflected in a map's center of gravity (Figure 2) or overall motor output (Figure III in the online-only Data Supplement), we generated a spatial autocorrelation index (Figure 5B) for all motor maps by calculating the correlation between pairs of pixel values (movement amplitude) separated by a given distance. Motor maps were more diffuse after motor-targeted stroke and especially after sensory-targeted strokes, with a decrease in correlation between neighboring pixels (Figure 5C and 5D). Local correlation was negatively correlated with infarct volume for sensory strokes (Pearson $r$=–0.89; $P$=0.04; n=6 mice) and motor strokes ($r$=–0.71; $P$=0.04; n=8 mice).

Motor maps were generated by stimulating cortical sites in a random spatial order, which raises the possibility that decreased spatial correlation after stroke arose from fluctuations in motor output over the course of an experiment. This was not the case, however, because performing linear regression on plots of cumulative motor output over the course of a mapping session revealed linear rates of motor output before and after stroke (Figure IV in the online-only Data Supplement). The diffuse structure of motor maps after stroke may instead be a manifestation of the ongoing reorganization of the underlying cortical circuitry, with the emergence of a new sFL map forcing mFL to either devote its neurons to a hybrid sensory/motor role or to become a mosaic of intermingled motor and sensory neurons (Figure 6).

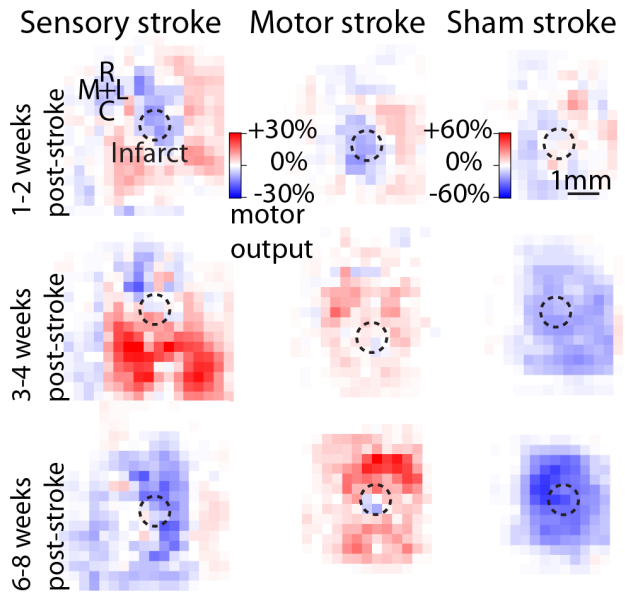


**Figure 4.** Stroke causes regional changes in motor excitability. Poststroke maps were normalized to their baseline average by division, and then maps from multiple animals were aligned according to the location of the infarct and averaged first across the group and then for the 2 time points indicated. Color scale denotes mean percentage change in movement amplitude relative to baseline. Scale at **left** applies to sensory and motor stroke groups, scale at **right** applies to sham stroke.

## Discussion

We have exploited the development of a new method for light-based motor mapping[12] to perform the first longitudinal study of sensorimotor reorganization after targeted stroke. Strokes targeted to a portion of forelimb motor cortex caused decreased motor output from the infarcted region that was offset by peri-infarct hyperexcitability, but did not affect the position or excitability of the sFL map. Sensory stroke displaced sFL maps toward the center of the mFL map, causing modest

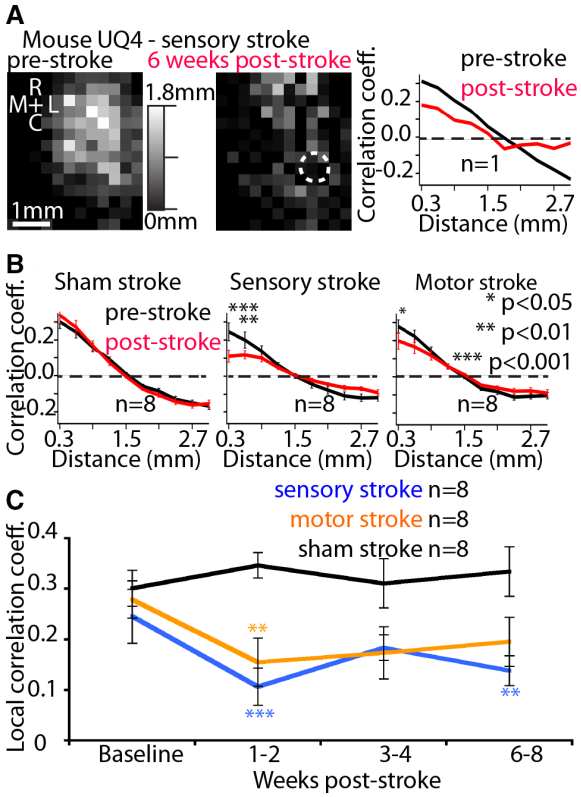


**Figure 5.** Poststroke reorganization causes motor maps to develop a diffuse structure. **A**, Representative motor maps obtained before and 6 weeks after a stroke targeted to sFL. After stroke, the map has a more scattered appearance, with greater variability between the amplitude of adjacent pixels. At **right**, spatial autocorrelation of representative motor map reveals decreased correlation between nearby pixels after stroke. **B**, Mean spatial correlations for each group. Bonferonni's post-test values marked for 2-way RM-ANOVA. **C**, Changes in correlation strength between adjacent pixels after stroke. Both sensory- and motor-targeted stroke caused lasting decreases in local correlation (2-way ANOVA; $F(2)=23.9$; $P<0.0001$; asterisks indicate $P$ values from Bonferonni's post test against the sham group).

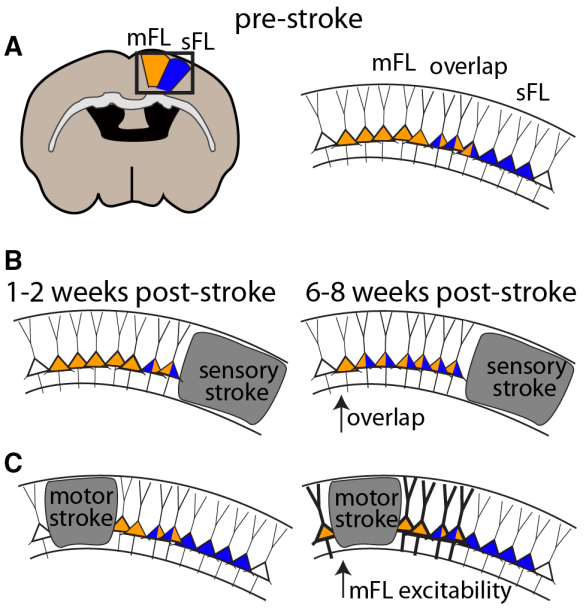


**Figure 6.** Model of cortical plasticity underlying sensorimotor map reorganization. **A**, Mouse sensorimotor cortex (box outlined in coronal section at **left**) is schematized as overlapping populations of motor (orange) and sensory (blue) neurons (**right**). **B**, After sensory stroke, the sensory region is initially destroyed (**left**), but the overlap region (represented with mixed orange/blue neurons) survives and expands to form the new sFL representation in motor cortex (**right**). **C**, Strokes in motor cortex do not cause the motor map to expand into sensory forelimb (sFL). Instead, an increase in the excitability of peri-infarct neurons (indicated with bold lines) compensates for the partial loss of motor forelimb (mFL).

secondary displacement of mFL that was strongly correlated with the extent of sFL shift but less than the map displacement seen after strokes within mFL itself. After sensory-targeted stroke in particular, motor map structure exhibited a diffuse structure that was not explained by fluctuating levels of motor output within an experiment. These data suggest that motor cortex is able to host new sensory representations without abandoning its cortical territory, albeit at the cost of manifest alterations to the motor cortical network. This pattern of reorganization may differ after larger strokes, particularly if the entire sensorimotor cortex was destroyed.

Remapping of cortical function is closely related to behavioral recovery.[17–19] In particular, recovery tends to be best in patients[20–23] or animal models[19,24,25] where reorganization occurs primarily within the perilesional cortex of the stroke-affected hemisphere, typically after incomplete lesions of motor cortex. Despite the fact that it does not produce a large penumbra,[26] the photothrombotic model is well suited to studying delayed reorganization in peri-infarct cortex. We observed that both motor and somatosensory maps initially displaced from their original location typically came to occupy the peri-infarct region (Figure 2). After strokes in motor cortex, peri-infarct cortex became hyperexcitable (ie, generated larger movements on stimulation than were observed during the prestroke baseline period), thereby preserving overall levels of motor output (Figure 4; Figures II and III in the online-only Data Supplement). Similar disinhibition of motor cortex occurs after stroke in human patients.[27] In contrast to the increased peri-infarct excitability seen after strokes in motor cortex, sham-operated mice exhibited a uniform decrease in motor excitability throughout the map area (Figure 4). This could be because of either changes in the viability of the cranial window over time or the effects of repeated anesthesia and stimulation of the periphery (during sensory mapping) or cortex (during motor mapping). The decreased excitability of sham mice makes the peri-infarct hyperexcitability seen after motor stroke even more striking. This is the first study of its kind involving longitudinal light-based motor mapping and as such it will need to be compared with future experiments using alternate surgical preparations or stimulation parameters to further address this question.

The diffuse structure of motor maps after stroke, evidenced by their decreased local spatial correlation (Figure 5), has not previously been reported. Maps may be altered by the incorporation of new regions of cortical output that were masked by inhibition before stroke.[28,29] Map area remains constant after stroke (Figure III in the online-only Data Supplement), but this could reflect the addition of new, more distant regions to the map offsetting the loss of motor output from the area

of the infarct (Figure 4; Figure II in the online-only Data Supplement). Curiously, the diffuse motor map structure was most pronounced after strokes targeted to sensory cortex. This could be because of an expanded region of motor cortex devoted to mixed sensory/motor function (Figure 6). After stroke, this region may contain more neurons performing a dual sensory/motor role[5] or an intermingled mixture of single-role neurons devoted solely to motor or sensory function. Either of these scenarios could account for the observation of diffuse motor map structure after stroke. Future studies could combine LBM with imaging of microscopic cellular structure and function after stroke to glean additional detail.

Strokes targeted to motor cortex caused an overall decrease in motor map area of ≈50% in the first week post stroke (Figure III in the online-only Data Supplement), but variability within groups prevented this trend from reaching statistical significance. In the cortical region immediately surrounding the infarct, motor output was significantly diminished (Figure II in the online-only Data Supplement) in the first month after stroke and recovered to baseline levels by 2 months. Motor output was not completely and permanently abolished from the vicinity of the infarct (Figures 1 and 4), perhaps because the infarcts were relatively small. It is possible that these small infarct volumes fostered plasticity by sparing the majority of sensorimotor cortex; larger lesions may result in reorganization predominantly within the contralesional hemisphere.[9] Individual microinfarcts, such as those created in this study (≈0.2 $mm^3$), may go unnoticed in a human brain, which is 3 orders of magnitude more massive than that of a mouse.[30] If scaled directly, these infarcts would still be only ≈0.7 $cm^3$ in a human, comparable with the lesion produced by a transient ischemic attack.[31] Transient ischemic attacks are known to cause increased cortical excitability in the affected hemisphere, which agrees with our findings.[32] We chose not to create larger infarcts because they were associated with elevated mortality rates; increasing the infarct size also decreases the amount of surviving cortex that can be studied within the limited area of the cranial window. In the future, bilateral studies of reorganization could take advantage of the spared hemisphere to expand the mapped area.[33] Performing motor mapping in the hours or days after stroke may also reveal greater reductions in motor output.[34]

We have demonstrated the feasibility of longitudinal sensorimotor mapping and characterized the spontaneous cortical reorganization that occurs in the absence of any intervention. It will now be possible to test the efficacy of preventative, protective, or rehabilitative therapies in the context of motor recovery, while monitoring the organization of sensorimotor cortex. Ultimately, these optimized rehabilitation strategies could be translated to humans to enhance recovery from stroke and other forms of brain injury.[35,36]



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## Disclosures

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## References

1. Liepert J, Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E, et al. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neurosci Lett*. 1998;250:5–8.
2. Murphy TH, Corbett D. Plasticity during stroke recovery: from synapse to behaviour. *Nat Rev Neurosci*. 2009;10:861–872.
3. Xerri C, Merzenich MM, Peterson BE, Jenkins W. Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *J Neurophysiol*. 1998;79:2119–2148.
4. Dancause N. Vicarious function of remote cortex following stroke: recent evidence from human and animal studies. *Neuroscientist*. 2006;12:489–499.
5. Winship IR, Murphy TH. *In vivo* calcium imaging reveals functional rewiring of single somatosensory neurons after stroke. *J Neurosci*. 2008;28:6592–6606.
6. Brown CE, Aminoltejari K, Erb H, Winship IR, Murphy TH. *In vivo* voltage-sensitive dye imaging in adult mice reveals that somatosensory maps lost to stroke are replaced over weeks by new structural and functional circuits with prolonged modes of activation within both the peri-infarct zone and distant sites. *J Neurosci*. 2009;29:1719–1734.
7. Witte OW, Stoll G. Delayed and remote effects of focal cortical infarctions: secondary damage and reactive plasticity. *Adv Neurol*. 1997;73:207–227.
8. Rijntjes M. Mechanisms of recovery in stroke patients with hemiparesis or aphasia: new insights, old questions and the meaning of therapies. *Curr Opin Neurol*. 2006;19:76–83.
9. Ward NS, Brown MM, Thompson AJ, Frackowiak RS. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain*. 2003;126(Pt 11):2476–2496.
10. Arenkiel BR, Peca J, Davison IG, Feliciano C, Deisseroth K, Augustine GJ, et al. *In vivo* light-induced activation of neural circuitry in transgenic mice expressing channelrhodopsin-2. *Neuron*. 2007;54:205–218.
11. Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nat Neurosci*. 2005;8:1263–1268.
12. Ayling OG, Harrison TC, Boyd JD, Goroshkov A, Murphy TH. Automated light-based mapping of motor cortex by photoactivation of channelrhodopsin-2 transgenic mice. *Nat Methods*. 2009;6:219–224.
13. Grinvald A, Lieke E, Frostig RD, Gilbert CD, Wiesel TN. Functional architecture of cortex revealed by optical imaging of intrinsic signals. *Nature*. 1986;324:361–364.
14. Harrison TC, Sigler A, Murphy TH. Simple and cost-effective hardware and software for functional brain mapping using intrinsic optical signal imaging. *J Neurosci Methods*. 2009;182:211–218.
15. Harrison TC, Ayling OG, Murphy TH. Distinct cortical circuit mechanisms for complex forelimb movement and motor map topography. *Neuron*. 2012;74:397–409.
16. Watson BD, Dietrich WD, Busto R, Wachtel MS, Ginsberg MD. Induction of reproducible brain infarction by photochemically initiated thrombosis. *Ann Neurol*. 1985;17:497–504.
17. Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, et al. A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke*. 1997;28:2518–2527.
18. Kolb B, Teskey GC. Age, experience, injury, and the changing brain. *Dev Psychobiol*. 2010;54:311–325.
19. van Meer MP, Otte WM, van der Marel K, Nijboer CH, Kavelaars A, van der Sprenkel JW, et al. Extent of bilateral neuronal network reorganization and functional recovery in relation to stroke severity. *J Neurosci*. 2012;32:4495–4507.
20. Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. *Brain*. 2002;125(Pt 12):2731–2742.
21. Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. The role of ipsilateral

premotor cortex in hand movement after stroke. *Proc Natl Acad Sci USA*. 2002;99:14518–14523.
22. Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. Reorganization of the human ipsilesional premotor cortex after stroke. *Brain*. 2004;127(Pt 4):747–758.
23. Cramer SC, Shah R, Juranek J, Crafton KR, Le V. Activity in the peri-infarct rim in relation to recovery from stroke. *Stroke*. 2006;37:111–115.
24. Dijkhuizen RM, Ren J, Mandeville JB, Wu O, Ozdag FM, Moskowitz MA, et al. Functional magnetic resonance imaging of reorganization in rat brain after stroke. *Proc Natl Acad Sci USA*. 2001;98:12766–12771.
25. Dijkhuizen RM, Singhal AB, Mandeville JB, Wu O, Halpern EF, Finklestein SP, et al. Correlation between brain reorganization, ischemic damage, and neurologic status after transient focal cerebral ischemia in rats: a functional magnetic resonance imaging study. *J Neurosci*. 2003;23:510–517.
26. Lee VM, Burdett NG, Carpenter TA, Hall LD, Pambakian PS, Patel S, et al. Evolution of photochemically induced focal cerebral ischemia in the rat magnetic resonance imaging and histology. *Stroke*. 1996;27:2110–2119.
27. Manganotti P, Acler M, Zanette GP, Smania N, Fiaschi A. Motor cortical disinhibition during early and late recovery after stroke. *Neurorehabil Neural Repair*. 2008;22:396–403.
28. Perez MA, Cohen LG. Interhemispheric inhibition between primary motor cortices: what have we learned? *J Physiol*. 2009;587 (Pt 4):725–726.
29. Margolis DJ, Lütcke H, Schulz K, Haiss F, Weber B, Kügler S, et al. Reorganization of cortical population activity imaged throughout long-term sensory deprivation. *Nat Neurosci*. 2012;15:1539–1546.
30. Shih AY, Blinder P, Tsai PS, Friedman B, Stanley G, Lyden PD, et al. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci*. 2013;16:55–63.
31. Oppenheim C, Lamy C, Touzé E, Calvet D, Hamon M, Mas JL, et al. Do transient ischemic attacks with diffusion-weighted imaging abnormalities correspond to brain infarctions? *Am J Neuroradiol*. 2006;27:1782–1787.
32. Edwards JD, Meehan SK, Levy AR, Teal PA, Linsdell MA, Boyd LA. Changes in intracortical excitability after transient ischemic attack are associated with ABCD² score. *Stroke*. 2011;42:728–733.
33. Barbay S, Guggenmos DJ, Nishibe M, Nudo RJ. Motor representations in the intact hemisphere of the rat are reduced after repetitive training of the impaired forelimb. *Neurorehabil Neural Repair*. 2013;27:381–384.
34. Anenberg E, Arstikaitis P, Niitsu Y, Boyd J, LeDue J, Murphy TH. Selective acute reductions in motor cortex function by targeted ischemia in channelrhodopsin-2 transgenic mice. *Soc Neurosci*. 2012.
35. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? *Neurorehabil Neural Repair*. 2012;26:923–931.
36. Martin JH. Systems neurobiology of restorative neurology and future directions for repair of the damaged motor systems. *Clin Neurol Neurosurg*. 2012;114:515–523.