Review

Remapping the Somatosensory Cortex after Stroke: Insight from Imaging the Synapse to Network

Ian R. Winship and Timothy H. Murphy

Together, thousands of neurons with similar function make up topographically oriented sensory cortex maps that represent contralateral body parts. Although this is an accepted model for the adult cortex, whether these same rules hold after stroke-induced damage is unclear. After stroke, sensory representations damaged by stroke remap onto nearby surviving neurons. Here, we review the process of sensory remapping after stroke at multiple levels ranging from the initial damage to synapses, to their rewiring and function in intact sensory circuits. We introduce a new approach using in vivo 2-photon calcium imaging to determine how the response properties of individual somatosensory cortex neurons are altered during remapping. One month after fore-limb-area stroke, normally highly limb-selective neurons in surviving peri-infarct areas exhibit remarkable flexibility and begin to process sensory stimuli from multiple limbs as remapping proceeds. Two months after stroke, neurons within remapped regions develop a stronger response preference. Thus, remapping is initiated by surviving neurons adopting new roles in addition to their usual function. Later in recovery, these remapped forelimb-responsive neurons become more selective, but their new topographical representation may encroach on map territories of neurons that process sensory stimuli from other body parts. Neurons responding to multiple limbs may reflect a transitory phase in the progression from their involvement in one sensorimotor function to a new function that replaces processing lost due to stroke.

Keywords: stroke; ischemia; 2-photon; intrinsic optical signals; plasticity; functional imaging; remapping; behavioral recovery; dendritic spine; regeneration

O ne of the most recognized principles of the primary somatosensory cortex states that sensory information from touch and proprioceptive receptors on one side of body is processed in the cortex on the opposite side of the brain (Buonomano and Merzenich 1998). The sensory representation for each body part occupies a particular cortical territory, resulting in a topographical somatotopic cortical map. These maps represent the aggregate behavior of thousands of sensory neurons tuned to somatosensory stimulation of that particular region of the periphery. Here, we describe how individual neurons within these maps adapt to replace the function of neurons and circuitry lost to the damaging effects of ischemic stroke. Ischemic stroke is caused by a transient or permanent reduction in blood

flow to the entire brain (global ischemia) or to specific territories of the brain (focal ischemia). Brain injury following ischemia results from a complex cascade of pathological events triggered by reduced blood flow to the affected tissue (Hossmann 2006). Although tissue death occurs within minutes to hours of the onset of reduced blood flow, functional recovery from stroke-induced brain injury continues weeks and months after the initial insult (Carmichael 2003). It has been suggested that this functional recovery occurs via adaptive plasticity in surviving neurons, whereby viable brain tissue reorganizes in order to rebuild or replace damaged synaptic connections and strengthen surviving neuronal networks (Carmichael 2003; Carmichael 2006; Coq and Xerri 1999; Dancause and others 2005; Nudo and Milliken 1996; Rouiller and others 1998). Indeed, it has been demonstrated in both human stroke patients and animal models of stroke that surviving regions of the cortex can adopt the motor- or sensory-processing functions of regions lost to damage (Castro-Alamancos and Borrel 1995; Dijkhuizen and others 2001; Dijkhuizen and others 2003; Rossini and others 2007; Schaechter and others 2006). Here, we review how adaptive plasticity at the level of individual neurons and local networks contributes to the cortical remapping thought to underlie behavioral recovery.

From the Department of Psychiatry (NRU), Centre for Neuroscience, University of Alberta, Edmonton, Alberta, Canada (IRW); and the Department of Psychiatry, Brain Research Centre, University of British Columbia, Vancouver, British Columbia, Canada (THM).

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Address correspondence to: Timothy H. Murphy, PhD, University of British Columbia, Department of Psychiatry, 4N1-2255 Wesbrook Mall, Vancouver, BC, Canada, V6T 1Z3; e-mail: thmurphy@interchange.ubc.ca.

Structural Damage at the Onset of Stroke Determines Circuits Available for Later Rewiring

Within the stroke core, widespread cell death occurs with complete loss of neuronal structure and function. Even over several weeks' time, there is little evidence for recovery of function within the core (Brown and others 2007; Winship and Murphy 2008). However, the capacity for repair and recovery is enhanced at the borders of the stroke core in the peri-infarct region. Here, focal stroke induces profound, but at times reversible, changes in synaptic structure of the peri-infarct neurons. These changes provide the framework under which individual neurons rewire during recovery. Changes in the structure and turnover rate of dendritic spines, the primary postsynaptic component of excitatory synapses in the brain, have been detected with in vivo 2-photon (or multiphoton) laser scanning microscopy to visualize the fine structure of neurons expressing fluorescent proteins (Grutzendler and others 2002; Holtmaat and others 2005; Trachtenberg and others 2002; Zuo and others 2005). Two-photon microscopy during acute ischemia demonstrated that severe (<20%) but not moderate reductions in blood flow (up to 50%) causes a rapid loss of spine and dendrite structure in individual neurons within as little as 2 to 10 minutes of stroke onset (Zhang and others 2005; Murphy and others 2008) (Fig. 1A). A similar loss of structure was seen in photothrombic occlusion, filament-induced middle cerebral artery blockade, and transient global ischemia (Zhang and others 2005; Murphy and others 2008; Li and Murphy 2008) (Fig. 1A-D). Importantly, these changes were not restricted to visualization by fluorescent proteins and were readily detected using Golgi histological staining (Brown and others 2008) (Fig. 1D). Damaged and undamaged dendrites were separated by a sharp border according to their proximity to the nearest flowing capillaries (Zhang and Murphy 2007). Normally, dendritic spines were on average 13 μm from flowing vessels (Zhang and others 2005); after stroke, intact dendrites were found on average 80 μm from flowing vessels, providing an estimate of the distance over which metabolic support can be extended. The damage to dendrites was not uniform within single neurons, as processes closest to ischemic zones and those within the apical dendritic tuft were damaged most severely (Enright and others 2007; Zhang and Murphy 2007) (Fig. 1C-D). Surprisingly, early dendrite and spine structural damage was ionotropic glutamate receptor independent (Murphy and others 2008), and structure was restored if reperfusion occurred even after prolonged (60 minutes) middle cerebral artery occlusion (MCAo) (Li and Murphy 2008) (Fig. 1C). We propose that these early structural changes are quite relevant to later recovery of function

because they determine which circuits are available to participate in the recovery process. A general theme derived from acute 2-photon imaging studies of stroke-induced damage is that the loss of circuitry is not necessarily complete within a single neuron. Conceivably, neurons or networks with partial function could be key substrates and mediators of remapped function.

Altered Excitation-Inhibition Balance and Synaptogenesis after Stroke

Providing the basis of remapped sensory function after stroke are specific changes in excitation-inhibition balance and synaptogenesis. Studies using animal models of focal stroke have identified long-lasting increases in neuronal excitability, with both excitatory and inhibitory neurotransmission altered by ischemia. N-methyl-D-aspartate (NMDA) receptor–mediated and non-NMDA receptor–mediated glutamate transmission are enhanced for up to 4 weeks after animal models of MCAo (Centonze and others 2007; Mittmann and others 1998), and the induction of long-term potentiation is facilitated in the perilesional cortex 7 days after focal cortical stroke (Hagemann and others 1998). Ischemia also induces a widespread and long-lasting impairment of inhibitory gamma-aminobutyric acid (GABA) transmission in both the peri-infarct cortex and in the hemisphere contralateral to the lesion after focal stroke (Buchkremer-Ratzmann and others 1996; Domann and others 1993; Schiene and others 1996). Studies of long-term recovery after experimental stroke have demonstrated that cortical hyperexcitablity peaks weeks after onset and persists for months after the initial insult (Domann and others 1993; Mittmann and others 1998; Schiene and others 1996). Long-lasting disinhibition of both the ipsilesional and contralesional hemispheres has also been reported in the clinical stroke population (Butefisch and others 2003; Manganotti and others 2008).

In vivo 2-photon imaging has also been used to demonstrate enhanced synaptogenesis during long-term recovery from stroke, as indicated by elevated spine formation (excitatory synapses) on the apical dendrites of layer 5 neurons in the peri-infarct cortex (<0.5 mm from the stroke border) for 6 weeks or more following stroke (Brown and others 2007, 2009; reviewed in Brown and others 2008). These data agree well with previous studies that identified axonal sprouting in the peri-infarct cortex (measured via GAP-43 expression) that is significantly enhanced for the first 2 weeks following ischemia and has been correlated with axonal regeneration (Carmichael and Chesselet 2002; Li and others 1998; Stroemer and others 1995). As recovery proceeds over several months, a progression from axonal sprouting to synaptogenesis is suggested by
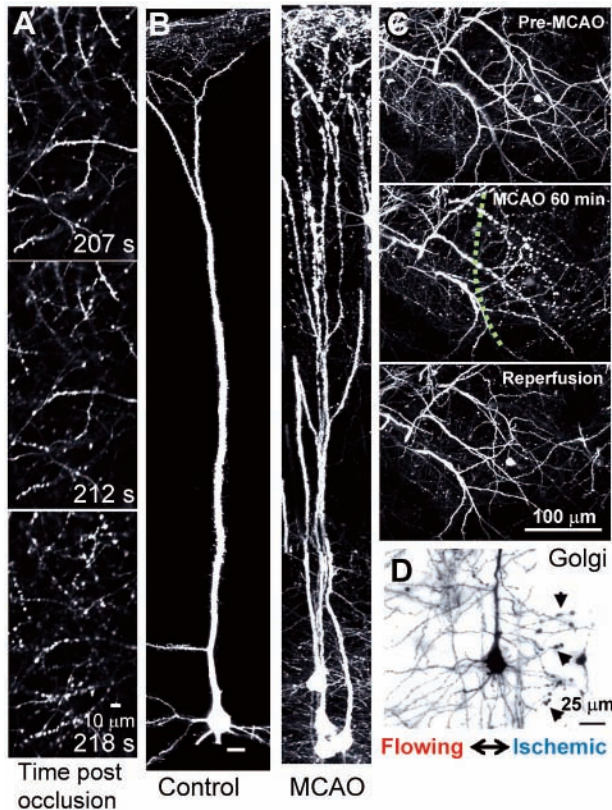
Figure 1. Stroke induces rapid and selective damage to brain circuitry. (**A**) Two-photon in vivo image taken from layer I within an adult GFP-M mouse somatosensory cortex at the given time points after induction of global ischemia. Between 207 and 212 seconds after ischemic induction, a collapse in dendritic structure and regions of beaded dendrites is apparent. Image is modified from Murphy and others 2008 and is used with permission from the Society for Neuroscience. (**B**) Stroke-induced changes in dendritic structure are observed in focal stroke models, including middle cerebral artery occlusion. The panel on the left shows a confocal image from a perfusion fixed and sectioned layer 5 cortical neuron with its apical dendrite and tuft in a region not subjected to ischemia. The neuron on the right is within the middle cerebral artery territory (2 hours after occlusion) and shows extensive beading within its apical tuft, but with relatively intact dendritic structure closer to the soma. Scale bar, 20 μm. Data shown are adapted from Enright and others 2007 and are used with permission from Nature Publishing Group. (**C**) Two-photon in vivo imaging performed from the surface scanning into the brain of an adult GFP-M transgenic mouse indicates selective regional vulnerability of dendrites to middle cerebral artery occlusion. In the second panel down, taken during occlusion, dendrites on the right side of the image are further within the middle cerebral artery territory and are more extensively beaded. The damage is partly reversible upon reperfusion after even 60 minutes of ischemia. Image is modified from Li and Murphy 2008 and is used with permission from the Society for Neuroscience. (**D**) Ischemic changes in dendritic structure are not limited to assessment using GFP and can be visualized using Golgi histology techniques on fixed and sectioned tissue. In this case, the cortical neuron shown was close to the infarct border with the left side of the neuron projecting towards areas with increased blood flow, while the right side (as shown) projects toward the center of the infarct. An increase in dendritic beading is apparent towards the center of the infarct (see arrowheads marking blebs). Image is modified from Brown and others 2008 and is used with permission from the American Heart Association.

an increase in synaptophysin immunoreactivity and a return to baseline GAP-43 levels (Carmichael 2003; Stroemer and others 1995), as well as an increase in dendritic growth and complexity (Biernaskie and Corbett 2001; Biernaskie and others 2004; Gonzalez and Kolb 2003). In addition to increased synaptogenesis, anatomical studies have demonstrated that local and distal intracortical projection patterns are altered by ischemia (Brown and others 2009; Carmichael and others 2001; Dancause and others 2005). A reorganization of intracortical projections after brain injury is supported by lesion studies in the visual cortex, which suggest that plasticity is intrinsic to the cortex (particularly long-range horizontal connections) and that reorganization of thalamocortical afferents alone cannot account for the cortical plasticity observed after lesion (Darian-Smith and Gilbert 1995; Gilbert 1998). Thus, results from animal studies show that processes set into motion after stroke alter both the wiring and physiology of the brain. These events promote plasticity that lead to remapping of function and potentially aid the recovery process. Before reviewing animal data on how these changes lead to the remapping of individual neurons, we review evidence that the general phenomenon of remapping is prevalent in the human clinical population and thus is a highly relevant topic for study.

Regional Remapping within the Poststroke Brain in the Human Clinical Population

While an investigation of functional plasticity in individual neurons and their circuitry is not possible in the human stroke population, topographical reorganization of the cortex has been demonstrated in stroke patients using a variety of methods (Rossini and others 2007). Magnetoencephelography (MEP) is a noninvasive method that measures changes in magnetic fields at the cortical surface generated by the summed activity over a region of the cortex. This technique has been used to demonstrate cortical plasticity within the primary somatosensory cortex in a stabilized clinical population greater than 1 year after stroke (Rossini and others 1998; Rossini 2001). These studies showed an expansion of the ipsilesional, primary sensory hand representation into regions not typically associated with hand somatosensation and raise questions about whether individual neurons within these areas would process both hand-specific signals as well as their previous function. Similarly, cortical reorganization in the motor cortex after stroke has been demonstrated in human patients using transcranial magnetic stimulation (TMS)–based motor mapping. TMS has been used in chronic stroke patients to categorize expansion, restriction, or migration of cortical maps (Cicinelli and others 1997;

Traversa and others 1997). Interestingly, physical therapy typically induces an increase in motor map size that correlates with significant functional improvement (Liepert and others 1998, 2000).

While TMS and MEP mapping provide excellent temporal resolution, they lack the 3-dimensional spatial resolution associated with modern functional imaging techniques. Despite their inability to observe the activity of individual neurons, functional imaging techniques such as positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI) can provide 3-dimensional maps of regional activity. PET and fMRI derive their signals from regional blood flow and metabolic changes closely associated with aggregate neuronal spiking in a given region of the brain and have proven effective in defining maps of regional brain activity with submillimeter resolution (Rossini and others 2007). These techniques have been used to demonstrate that patients with stroke-induced sensorimotor impairments show altered patterns of both ipsilesional and contralesional cortical activation after stroke (Calautti and Baron 2003; Carey and others 2002; Chollet and others 1991; Cramer and others 1997; Cramer and Bastings 2000; Herholz and Heiss 2000; Jaillard and others 2005; Nelles and others 1999a, 1999b; Seitz and others 1998; Ward and others 2003a, 2003b, 2006; Weiller and others 1993). When discussing cortical activation, studies typically refer to changes with respect to the stroke-affected limb (e.g., stimulating the left limb of an animal having a stroke on the right side). Assuming relatively preserved crossed sensory pathways, stimulating the stroke-affected limb would trigger ipsilesional activation within the contralateral sensory cortex (i.e., right cortical activation after stimulation of the left limb). Contralesional activation would involve stimulation of the stroke-affected limb (the left limb of a patient with right-hemisphere stroke), with the response observed opposite to the lesion on the left side of the brain. Most notably, increased activation in novel ipsilesional sensorimotor areas is correlated with improved behavioral recovery in human stroke patients (Fridman and others 2004; Johansen-Berg and others 2002a, 2002b), whereas contralesional activation, particularly in the supplementary motor cortex, is associated with poor recovery (Calautti and Baron 2003; Schaechter 2004). In some cases, increased contralesional activity occurs because the ipsilesional hemisphere may be extensively damaged, limiting the amount of viable tissue available for plasticity. Therefore, observations of contralesional activation leading to a poor recovery prognosis may be more related to the severity of the initial insult and not necessarily something detrimental about the activity itself.

In terms of linking structural and functional alterations, MRI performed in a group of chronic hemiparetic stroke patients (Schaechter and others 2006) has demonstrated that these patients show increased activation of the ventral postcentral gyrus in response to unilateral tactile stimulation. Strikingly, this same region showed an increase in cortical thickness relative to healthy controls, providing structural evidence of plasticity colocalized with functional rewiring in the human brain after stroke.

Regional Remapping of the Poststroke Brain in Animal Models of Stroke

Because the human patient population presents with confounding heterogeneity in the location and extent of brain injury, much of what is known about the mechanisms of poststroke functional plasticity comes from animal models of stroke. Dijkhuizen and others (2001, 2003) performed fMRI during forelimb stimulation of rats at different time points (day 1, 3, or 14) after unilateral MCA occlusion and demonstrated increased activation of the contralesional hemisphere by stimulation of the stroke-affected limb 3 days after stroke. Similarly, Abo and others (2001) demonstrated increased contralesional sensorimotor activation elicited by stimulation of the stroke-affected limb 21 days after unilateral photothrombotic infarction of the sensorimotor cortex. However, contralesional activation due to stimulation of the stroke-affected limb is not observed in all cases (Weber and others 2008), and functional recovery has been correlated with the emergence or restoration of somatosensory activation in the peri-infarct cortex (i.e., within or near the original sensorimotor regions) (Dijkhuizen and others 2001, 2003; Weber and others 2008). fMRI also permits an analysis of changes in neuroanatomical connectivity after stroke via manganese-enhanced, MRI-based neuronal tract tracing (van der Zijden and others 2007, 2008). Manganese injection in the perilesional cortex after MCA occlusion reveals an initial disruption of ipsilateral sensorimotor connectivity early after stroke but an eventual restoration of ipsilateral connectivity and enhanced interhemispheric connectivity associated with improved sensorimotor function.

While fMRI can be used to provide millimeter-scale 3-dimensional maps of brain activation before and after stroke, maps of regional activation on the surface of the cortex can be attained with high spatial (~50-100 μm) and temporal resolution by imaging the sensory-evoked intrinsic optical signal (IOS) (Bonhoeffer and Grinvald 1996; Frostig and others 1990). IOS imaging measures minute differences in light reflectance between active and inactive neuronal tissue and largely reflects hemodynamics (Bonhoeffer and Grinvald 1996; Devor and others 2003; Grinvald and others 1986; Winship and others 2007). Cortical maps based on the sensory-evoked IOS can be used to define the regions of the cortex activated by sensory stimulation and thus can be used to map plasticity in the sensory cortex after focal stroke.
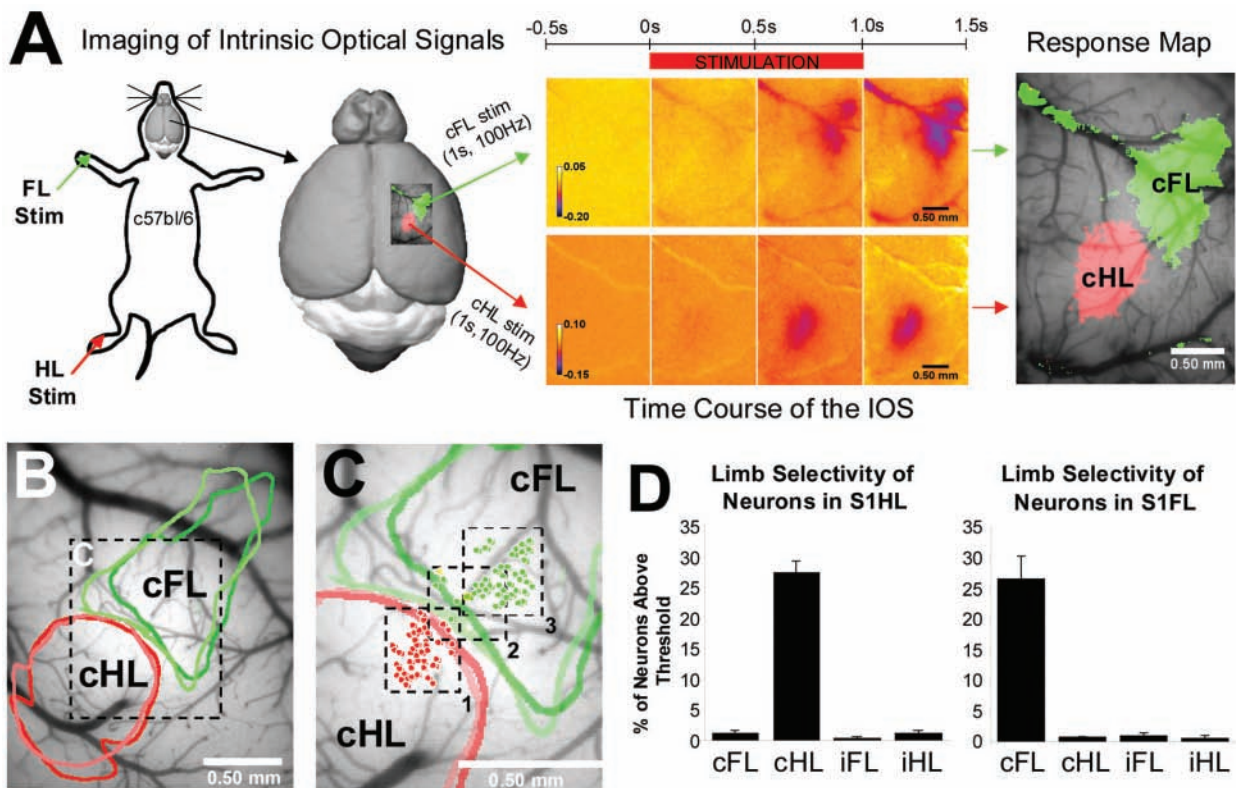
Figure 2. Imaging protocol and experimental timeline. (**A**) Vibrotactile stimulation (1 second, 100 Hz) of the cFL or cHL during imaging of IOS was used to define S1FL and S1HL, respectively. The time course and regional distribution of the IOS response to cFL (top) and cHL (bottom) stimulation, shown as a percentage change in light intensity, are shown. IOS response maps were thresholded at 50% of peak response amplitude and merged with an image of the surface vasculature to create maps of cFL and cHL activation. (**B**) IOS maps in a control mouse before and after the sham procedure reveal a consistent topography of cHL- and cFL-activated cortex. The borders of the presham and postsham IOS response maps from cHL and cFL stimulation (light red/green lines demonstrated presham borders; dark red/green lines demonstrated postsham borders). (**C**) Two-photon Ca^{2+} imaging was performed at 3 locations (1-3, demarcated by dashed white boxes) spanning the border between cHL- and cFL-activated cortex in cortical layer 2. A threshold analysis of somatic responses was performed, and the locations of responding neurons are superimposed on the map of the IOS response borders. Green dots show the location of neurons with above-threshold responses to cFL stimulation, and red dots show the location of cHL-activated neurons. Two-photon Ca^{2+} imaging revealed an extremely sharp border at the cellular level, with no spatial overlap between neurons sensitive to cHL or cFL stimulation. (**D**) Graphs show the prevalence of above-threshold responses to limb stimulation in S1HL (2282 neurons) and S1FL (1498 neurons), respectively, in control animals. From Winship and Murphy 2008, used with permission of the authors and publisher (Society for Neuroscience).

Figures 2A-B and 3A-C show maps of the sensory-evoked IOS acquired from control mice during vibrotactile stimulation of the contralateral forelimb and hindlimb (cFL and cHL, respectively). Decreased reflectance (Fig. 2A, middle), likely due to increasing deoxyhemoglobin in active regions, was used to define the forelimb and hindlimb primary somatosensory representations (S1FL and S1HL, respectively; far right) (Winship and Murphy 2008). Importantly, this stereotypical topography with sharp borders between S1FL and S1HL representations was consistent across mice and stable over time (Fig. 2B). To induce stroke, the S1FL was targeted for photothrombotic infarction (Fig. 3A-C). Photothrombosis involves the injection of a photosensitive dye (Watson and others 1985) and targeted illumination allowing for defined and reproducible ischemic lesions (Brown and others 2007, 2008, 2009; Winship and Murphy 2008; Zhang and others 2005). An advantage of photothrombosis

is that local small arterioles are primarily affected, permitting the location of stroke damage to be targeted and not necessarily dependent on the angioarchitecture of potentially variable large-surface arteries (Fig. 3A). Not surprisingly, 2 weeks after photothrombosis, little or no remapped cFL-evoked IOS signal is detected, while the S1HL representation remains relatively unperturbed (Winship and Murphy 2008). However, following longer recovery periods, novel patterns of activation in the cFL-evoked IOS were detected in the perilesional cortex. Targeted photothrombotic stroke was associated with a shifted S1FL representation 1 and 2 months after stroke, with S1FL shifted medial and posterior to the stroke and original S1FL territory. As illustrated in Figure 4A and E, clear cFL-evoked activation of a region of the cortex posterolateral to the S1HL was observed 1 to 2 months after stroke but not in controls. In Figure 4E, the infarction occupies the center of the prestroke S1FL and is not
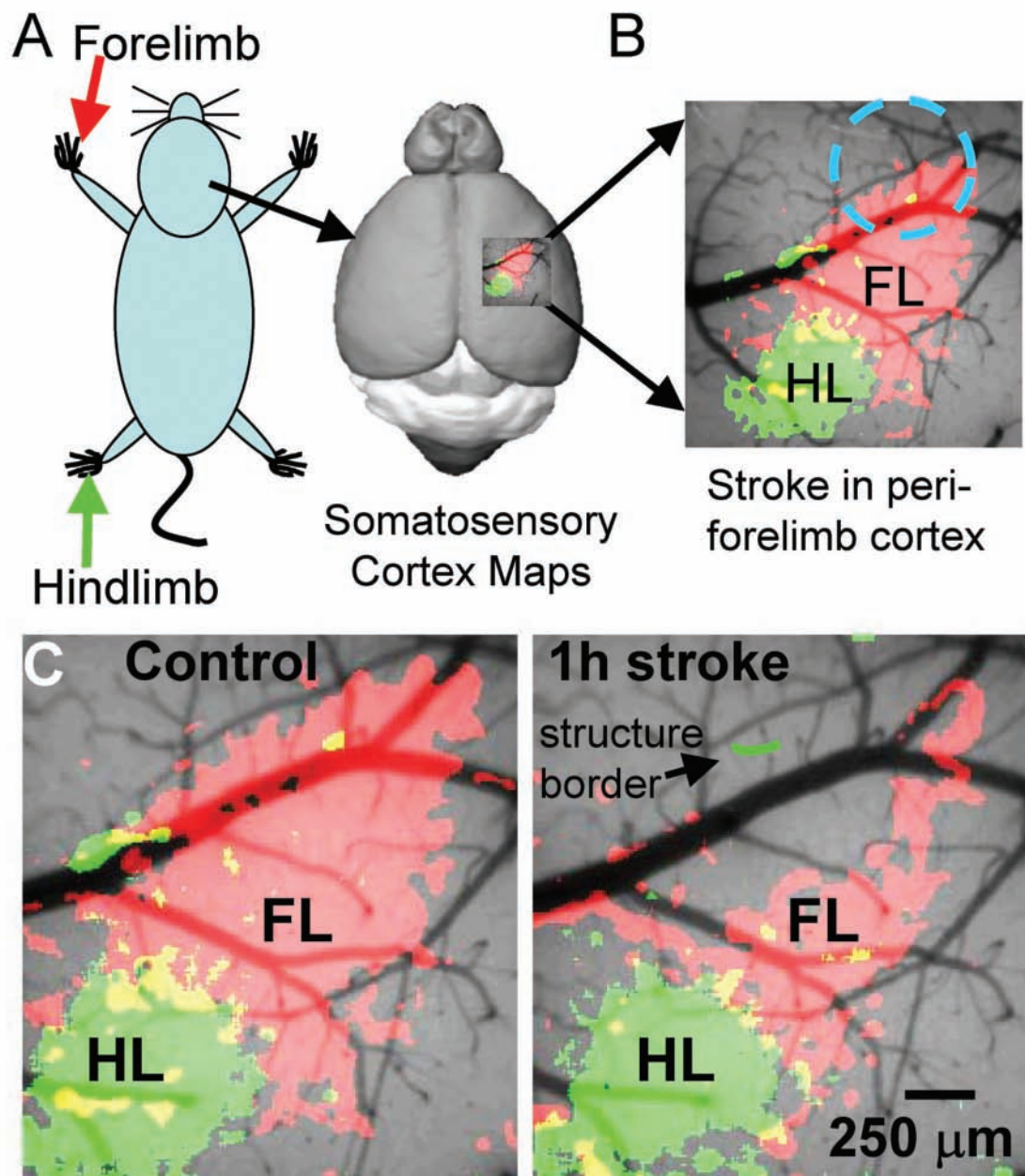
Figure 3. Targeted ischemia using photothrombosis to a subset of the forelimb sensory map. (**A**) Cartoon showing mouse subjected to either contralateral forelimb or hindlimb stimulation. Using intrinsic optical signal imaging, these sensory areas can be mapped and superimposed over an image of the blood vessels. (**B**) A subset of the forelimb map was targeted for photothrombosis (light-induced clotting). (**C**) Changes in sensory maps 1 hour after targeted photothrombosis. These results indicate that photothrombosis can be selective and affect a subset of a sensory domain, providing some spared networks, which could potentially relay forelimb-specific signals and mediate wide-scale remapping and recovery of function at later time points. The area where the transition from damaged to intact dendrites occurred is indicated by a green line (structure border). Below this line, a region ~400 μm in width was found with intact structure existing but little IOS response. This area could be recruited during later structural plasticity and regain activity after angiogenesis and restoration of full blood flow. Used with permission from Zhang and Murphy 2007.

activated by cFL stimulation. A new pattern of cFL-evoked activity in the peri-infarct rim extends further in anterior, medial, and posterior directions relative to the prestroke representation. In comparison to controls (Fig. 2A-C), the borders between S1HL and S1FL appear blurred 1 month after stroke, with significant overlap between the cHL- and cFL-evoked IOS maps (Fig. 4A, E, yellow shading). Because IOS imaging reflects an indirect hemodynamic measure of neuronal activity, regional imaging of voltage-sensitive dyes was recently used to directly measure sensory-evoked depolarization (Brown and others 2009). This study confirmed the
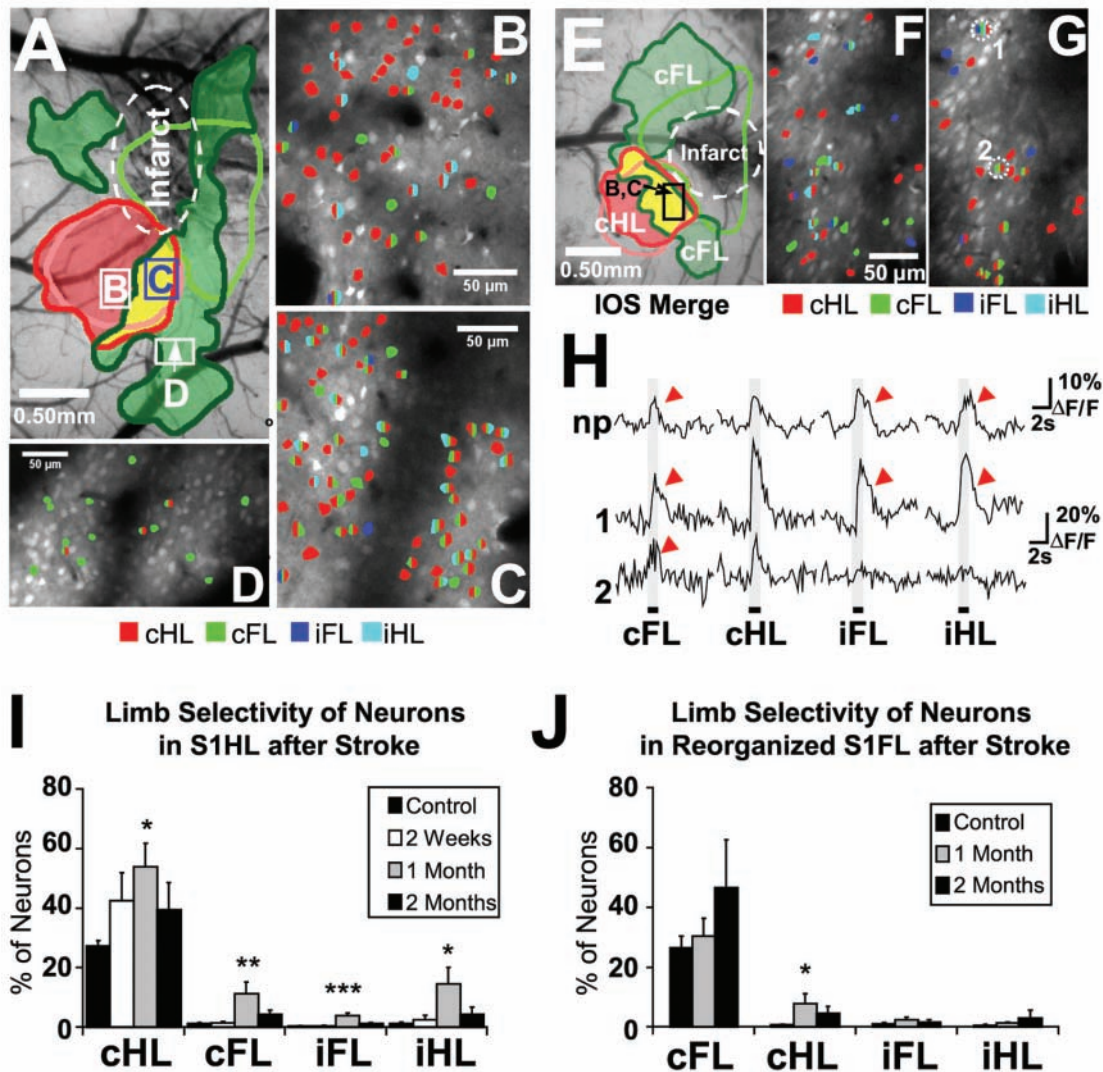
Figure 4. Regional and single cell rewiring after stroke. (**A, E**) Prestroke and poststroke maps of the sensory-evoked IOS in mouse *Str22* and *Str25,* each imaged 1 month after targeted photothrombotic infarction of S1FL. Prior to stroke, the IOS evoked by cFL and cHL stimulation had typical topography with a sharp border between the limb representations (cHL- and cFL-responsive regions demarcated by red and green lines without shading, respectively). After stroke, a new pattern of cFL-evoked IOS activity is observed (green shading), while cHL-evoked activity is preserved (red shading). Considerable overlap exists between cHL- and cFL-evoked IOS activity (yellow shading). (**B-D**) Representative 2-photon Ca^{2+} imaging data from the regions demarcated in **A**. Neuronal response maps (showing above-threshold somatic Ca^{2+} responses to different limbs, coded by color) are illustrated for each region. Maps in the core of S1HL (**B**) and in regions of IOS overlap (**C**) demonstrated reduced limb selectivity (most prominent in regions of IOS overlap). Response maps in **D** demonstrate that neurons in posterior regions of remapped S1FL are responsive to cFL stimulation (such responses are not observed in this region of control animals). (**F-H**) Representative 2-photon Ca^{2+} imaging data from region demarcated in **E**. (**F, G**) Neuronal response maps (showing above-threshold somatic Ca^{2+} responses to different limbs, coded by color) at 2 depths are illustrated. (**H**) Ca^{2+} traces (averaged from 10 trials) for 2 neurons and the mean neuropil (np) response (from the image plane shown in **G**). Note the aberrant (nonselective) response to nonpreferred limbs (red arrowheads) in the representative traces and the reduced limb selectivity in the neuronal response maps. (**I**) The average prevalence of above-threshold neuronal Ca^{2+} responses to different limbs for neurons in the S1HL for all control and stroke animals. Multivariate analysis revealed a significant effect of stroke on limb selectivity ($P = 0.003$) in S1HL, and a univariate test showed that this effect was significant for all limbs ($P = 0.045$; cFL, $P = 0.007$; iFL, $P < 0.001$; iHL, $P = 0.015$). (**J**) Multivariate analysis of the prevalence of above-threshold somatic Ca^{2+} transients in neurons in S1FL revealed a weak effect of stroke on limb selectivity in reorganized S1FL ($P = 0.051$). Univariate tests revealed a significant increase in cHL-evoked responses in reorganized S1FL ($P = 0.043$). From Winship and Murphy 2008, used with permission of the authors and publisher (Society for Neuroscience).

pattern of S1FL remapping described with IOS imaging by Winship and Murphy (2008) and demonstrated that forelimb-evoked depolarizations found in S1HL 2 months after stroke involved perseverant activation with

durations 300% to 400% longer than controls. In support of these findings demonstrating remapping after focal ischemic insult, Zepeda and others (2003, 2004) demonstrated that retinotopic IOS maps in the visual cortex
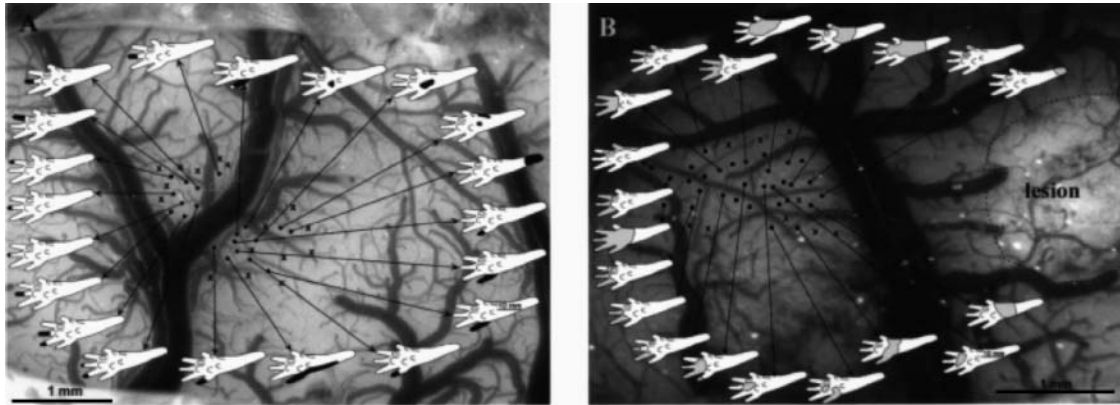
Figure 5. Enlarged receptive fields after focal stroke. Examples of receptive fields on the hindpaw skin of somatosensory cortical neurons recorded in (**A**) the right hemisphere of a normal, control animal and in (**B**) the right hemisphere of a rat with a photothrombotic lesion in the right hemisphere 1.5 mm caudal to the hindpaw representation. The border of the lesion is marked by a dotted line. Recordings were made 7 days after induction of the lesion. Shown is the dorsal surface of the cortex with blood vessels. Dots indicate penetration sites in the representation of the hindpaw. The arrows connect each penetration site with its corresponding receptive field, drawn as shading in a figurine of the left (**A, B**) hindpaw. (**A, B**) Frontal is on the left, and the sutura sagitalis is near the bottom. Scale bar, 1 mm. From Reinecke and others 2003, used with permission of the authors and publisher (Wiley-Blackwell).

reorganized within the peri-infarct region to compensate for loss of visual representation by increasing the area of visual space represented within the surviving cortex. Similarly, Wei and others (2001) reported that whisker cortical representations were shifted rostrally 30 days after ligation of branches of the MCA. Thus, IOS imaging demonstrates that the regional functional representation of tissue lost to stroke is remapped to other regions of the ipsilesional cortex, consistent with clinical data and other animal models suggesting that ipsilesional plasticity is important for functional recovery (Dijkhuizen and others 2001, 2003).

Remapping of the primary motor cortex following focal stroke has been investigated in animal models using motor-mapping techniques that employ intracortical microstimulation (ICMS) (Castro-Alamancos and Borrel 1995; Friel and others 2000; Frost and others 2003; Gharbawie and others 2005; Kleim and others 2003; Nudo and Milliken 1996; Remple and others 2001). As with TMS in the human stroke population, this method provides detailed information on motor-evoked potentials after stroke, but spatial resolution is limited. ICMS studies have shown that remapping of the primary motor cortex is experience dependent (Frost and others 2003; Kleim and others 2003; Nudo and Milliken 1996; Remple and others 2001) and that ablation of the remapped cortex reinstates behavioral impairments (Castro-Alamancos and Borrel 1995).

Functional imaging and ICMS provide powerful means to analyze regional remapping of the sensory and motor cortices after injuries such as stroke. However, these techniques measure aggregate activity in relatively large samples of tissue. As such, they are measures of regional plasticity lacking the spatial resolution to define how single neurons or local neuronal ensembles alter

their activity. Because current single-cell electrophysiological methods are technically demanding and time consuming (Brecht and others 2004; Waters and Helmchen 2006), few studies have examined the poststroke stimulus-evoked activity of identified neurons in vivo, and none has assessed the properties of these neurons with high resolution relative to reorganized regional maps. Single-unit extracellular recordings during sensory stimulation have been performed and have revealed enlarged receptive fields in neurons in peri-infarct tissue in both the visual (Eysel and Schweigart 1999; Schweigart and Eysel 2002) and somatosensory (Jenkins and Merzenich 1987; Reinecke and others 2003) cortices. In monkeys, Jenkins and Merzenich (1987) reported that loss of the palm representation in the somatosensory cortex was compensated for by enlargement of receptive fields in neurons adjacent to the cortical infarct. Reinecke and others (2003) performed single-unit extracellular recordings 7 days after photothrombotic insult posterior to S1HL and demonstrated that S1HL neurons which were sensitive to "just visible skin indentation" of the contralateral hindpaw possessed receptive fields approximately twice as large as neurons in the S1HL of control animals (Fig. 5A-B). Similar increases in cutaneous receptive field size were observed in contralesional S1HL, providing support for widespread disinhibition suggested by previous studies (Redecker and others 2002).

Approaches to Visualize Activity within Single Neurons In Vivo

While multiple electrode penetrations allow crude mapping of neuronal responses, this technique does not allow for high-resolution maps of neuronal activity

or unambiguous recording of identified local ensembles of neurons. Furthermore, tissue damage due to repeated electrode tracks makes it difficult to preserve the structural and functional integrity of individual neurons. The issue of tissue damage is particularly apparent with electrode arrays which displace a considerable volume of the cortex. At present, only 2-photon microscopy (Rochefort and others 2008; Stosiek and others 2003) permits high-resolution, real-time imaging of structure and function within identified neurons in vivo.

Recently, new techniques have enabled researchers to label thousands of cells in layers 2 and 3 of the cortex with membrane-permeable, fluorescent calcium indicators (Kerr and Denk 2008; Stosiek and others 2003). These small molecules, typified by Oregon green BAPTA-1 and fluo-4, have better signal-to-noise properties than current protein-based calcium indicators (Mao and others 2008)**.** By performing 2-photon imaging during sensory stimulation, calcium signals in dye-loaded neuronal somata can be detected. These signals reflect action potential firing (Berger and others 2007; Sato and others 2007; Stosiek and others 2003), enabling concurrent assessment of sensory-evoked suprathreshold spiking activity and precise spatial location of hundreds of neurons. Further, if dextran-conjugated calcium indicators are loaded by local electroporation, calcium imaging can be performed with subcellular resolution including dendritic spines or axon boutons (Nagayama and others 2007). Two-photon calcium imaging has already been used to investigate the input and output characteristics and fine spatial organization of cortical neuronal networks (Kerr and others 2005) and demonstrates the existence of sensory-evoked calcium signals in cortical astrocytes (Schummers and others 2008; Wang and others 2006; Winship and others 2007). More recently, 2-photon calcium imaging has revealed homeostatic regulation of plasticity in neurons within the visual cortex after monocular deprivation (Mrsic-Flogel and others 2007) and behaviorally correlated somatic calcium transients in neurons in the sensorimotor cortex of awake, head-restrained mice during locomotion (Dombeck and others 2007). Two-photon calcium imaging has also been used to reveal the precise functional microarchitecture of neurons in layer 2/3 of the visual cortex. In rats, neurons in the visual cortex demonstrated robust direction selectivity but no discernible organizational structure (Ohki and others 2005). In the visual cortex of cats, however, preferences for stimulus direction were segregated with precise columnar organization into discrete orientation columns with columnar borders only 1 to 2 neuronal somata wide (Ohki and others 2005, 2006). Interestingly, these sharp functional borders exist on a finer spatial scale than their dendritic arbors, which overlap with those of neighboring neurons. Discrete functional segregation without anatomical separation must therefore result from selective connectivity or uneven weighting of synaptic strength on either side of the border.

Sharp functional borders with precise cellular microarchitecture were also recently revealed in the somatosensory cortex of mice using 2-photon calcium imaging (Winship and Murphy 2008). Microinjections of membrane-permeable calcium indicators (Stosiek and others 2003) spanning the border of the S1HL and S1FL were made, and in vivo 2-photon calcium imaging during vibrotactile limb stimulation was used to categorize neurons according to limb preference. The spatial organization of responsive neuronal somata, color-coded by limb preference, from a representative animal is superimposed onto a map of the surface vasculature in Figure 2C. With rare exceptions, neurons near the border between S1FL and S1HL were completely selective for their preferred limb. Furthermore, somata were organized into a precise cellular architecture, with a sharp border between S1FL and S1HL and no overlap between cHL- and cFL-responsive neuronal somata, which precisely matched the regional maps defined by IOS imaging (Fig. 2C-D). The ability to resolve responses in individual neurons offers the possibility of understanding how individual neurons contribute to reorganized regional sensory maps.

Functional Rewiring of Single Neurons in the Poststroke Brain in Animal Models of Stroke

In order to investigate how focal ischemic insult altered limb selectivity and functional segregation at the level of individual layer 2/3 neurons, IOS imaging and 2-photon calcium imaging were performed in the somatosensory cortex of mice with targeted photothrombotic lesions of the S1FL (Winship and Murphy 2008). As described previously, regional IOS imaging revealed cFL-evoked activation of a region of the cortex posterolateral to the S1HL 1 to 2 months after stroke but not in controls (compare Fig. 2A-B to Fig. 4A, E). To investigate single-neuron response characteristics within these remapped forelimb representations, targeted microinjections of bulk-loading calcium indicator (Stosiek and others 2003) were made. Two-photon calcium imaging confirmed that neurons in this posterior extension of the remapped S1FL representation exhibited cFL-evoked calcium signals during sensory stimulation (Fig. 4D). As in control S1FL, neurons within this new S1FL representation were primarily selective for cFL stimulation, although some nonselective responses were observed. A comparison to cFL-evoked activity in single neurons in layer 2/3 of the corresponding region in control animals

confirmed that the remapped cFL-evoked activity is a function of stroke-induced plasticity, as strong responses to cFL movement were not identified in control animals (Winship and Murphy 2008). These data provide evidence that the limb specificity of individual neurons can be rewired but do not reveal whether the original function of the rewired neurons was altered.

As noted, IOS imaging suggested that the borders between S1FL and S1HL were blurred after stroke (Fig. 4A, E, yellow shading). To better understand how individual neurons altered their responses, 2-photon calcium imaging was used to examine regions of the remapped cFL representation impinging upon the original cHL-evoked map. Targeted microinjections of calcium indicator into these regions of apparent overlap permitted an analysis of sensory processing in single neurons and assessment of whether individual neurons would show tuning related to the cFL, cHL, or both limbs. Neuronal response maps in Figure 4A-D show that limb selectivity was altered throughout S1HL but was most pronounced in regions of cFL/cHL IOS map overlap. Note the abundance of individual neurons exhibiting suprathreshold calcium responses to stimulation of multiple limbs in the blurred functional border. Figure 4F-H shows 2-photon calcium imaging data from the region of IOS overlap demarcated by the black box in Figure 4E. Surprisingly, some neurons exhibited suprathreshold responses to test stimulation of all 4 limbs individually (neuron 1) or both contralateral limbs (neuron 2); nonselective responses such as these were exceedingly rare in control animals. Single-neuron somatosensory response maps from this region of S1HL/S1FL overlap are shown in Figure 4F-G. Again, reduced limb selectivity is apparent, as suprathreshold responses to stimulation of all limbs are represented within the maps, and many neurons respond to more than one limb (see neurons color-coded by selectivity). The altered neuronal organization (defined by somatic calcium transients) illustrated in Figure 4C, F, and G contrasts with the clearly defined border of control animals (Fig. 2C). It is conceivable that neurons at borders receive mixed subthreshold inputs to begin with and are therefore more malleable (Dragoi and others 2001; Schummers and others 2002). Nonselective activity in the neuropil (Fig. 4H) suggests that functional rewiring alters both presynaptic and postsynaptic activity (Kerr and others 2005).

In total, neuronal somatosensory response properties were assessed in nearly 6000 neurons after focal S1FL stroke (Winship and Murphy 2008). Figure 4I shows the percentage of neurons responding to stimulation of each of the limbs in S1HL over the 2 months following S1FL photothrombosis. Alterations of limb selectivity peaked 1 month after targeted ischemic insult and suggested a development of increased response selectivity at 2 months (Fig. 4I). Relative to

controls, the prevalence of neurons in S1HL stimulated by movement of more than one limb was greatly increased. In control S1HL, an average of 28.2% of neurons respond to stimulation of a single limb, 1.3% to stimulation of 2 limbs (individually), and 0.1% to stimulation of 3 or more limbs. Contrasting this, at 1 month poststroke, the percentage of neurons with above-threshold responses to 1, 2, or 3 or more limbs was 45%, 15%, and 5%, respectively. Averaging all poststroke time points, the prevalence of suprathreshold responses to 1, 2, or 3 or more limbs increased to 144%, 591%, and 1620% of controls, respectively.

The prevalence of suprathreshold responses to limb stimulation in S1FL of control and stroke animals is shown in Figure 4J (Winship and Murphy 2008). Averaging 1- and 2-month poststroke data, the prevalence of suprathreshold responses to cHL stimulation alone in S1FL was 609% that of controls, and the prevalence of neurons responding to both cHL and cFL stimulation was 1396% of control levels. Hence, 2-photon calcium imaging revealed that functional remapping may be facilitated by enhanced receptive fields in individual peri-infarct neurons, particularly in neurons near map boundaries. One month after stroke, neurons that were previously highly selective for a preferred limb processed information from multiple limbs, and the precise functional segregation typical of control animals was disrupted. However, during longer recovery (2 months), individual neurons developed more specific response characteristics and returned to a defined limb preference.

A Putative Role for Latent Subthreshold Connections as well as Synaptogenesis in Remapping after Stroke

Models detailing how anatomical and physiological alterations after stroke could account for functional rewiring at the regional and single neuron level are presented in Figures 6 and 7. The general theme is that a combination of unmasking latent subthreshold inputs as well as new synaptogenesis leads to remapping of function from damaged areas to peri-infarct surviving tissue. This model is supported by the observation that layer 2/3 neurons in unlesioned S1FL and S1HL receive subthreshold synaptic inputs from nonpreferred limbs (Ferezou and others 2007). While the suprathreshold receptive fields of spiking neurons in the somatosensory cortex are tightly tuned to a preferred stimulus, subthreshold changes in membrane potential (Berger and others 2007) have broadly tuned receptive fields. As noted, 2-photon calcium imaging detects intracellular calcium signals elicited by action potentials in neuronal somata and is relatively insensitive to subthreshold activity (Stosiek and others 2003; Berger
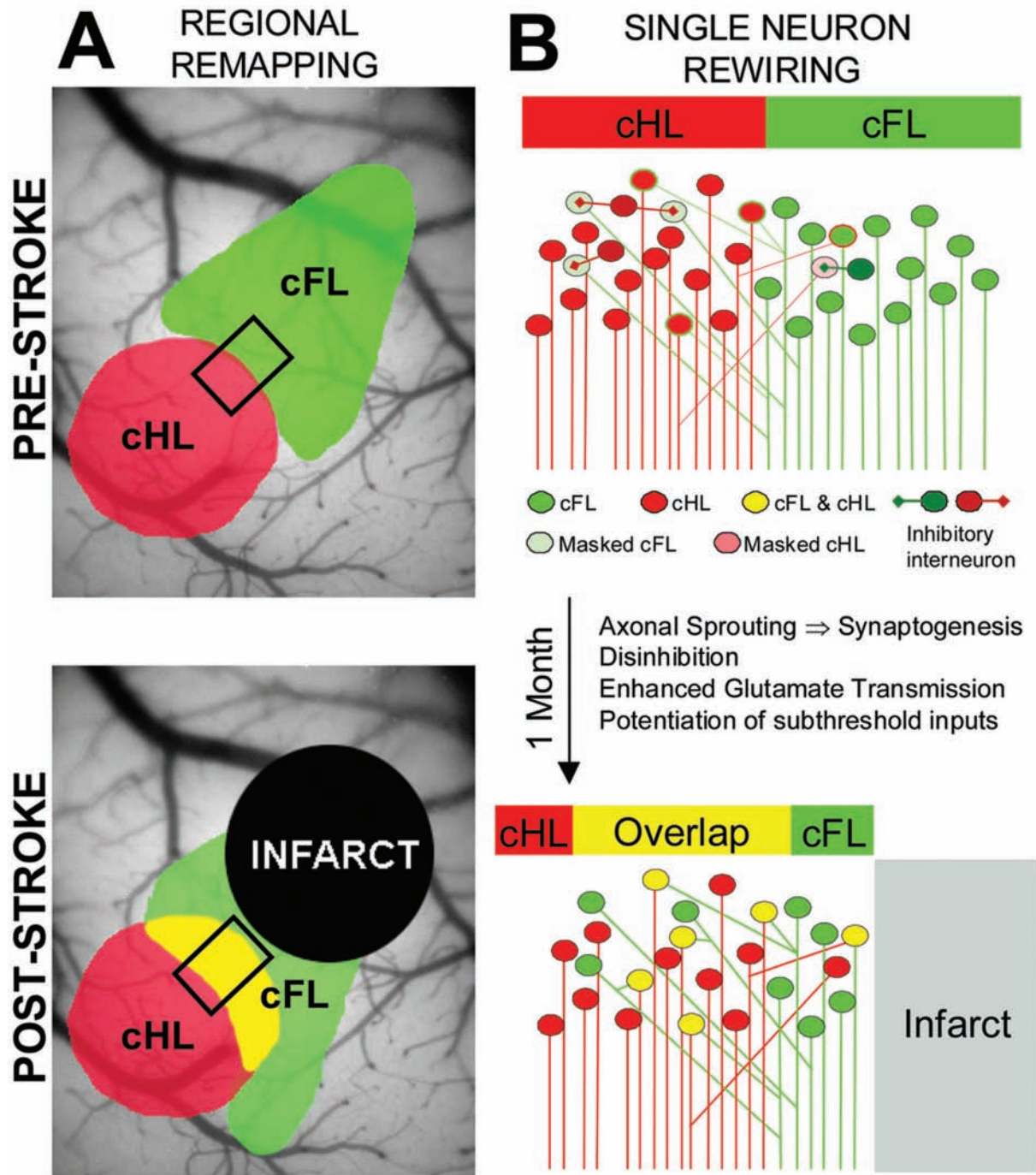
Figure 6. Model for remapping of sensory function after stroke at the level of individual neurons. (**A**) Normal contralateral forelimb- and hindlimb-stimulated sensory maps in mouse exhibiting sharp boundaries between territories, indicating specificity for suprathreshold neuronal activity (schematic example maps are shown). Bottom panel: Affect of forelimb area–targeted infarction on sensory map. Simplified example shown for period 1 to 2 months' poststroke with a loss of contralateral forelimb activity within the infarct core and a remapping of forelimb activity into the hindlimb map and more posterior regions. Yellow color indicates overlap between forelimb and hindlimb maps (green dots represent cFL-responsive neurons and red cHL), which is increased during stroke recovery. (**B**) Examples of single-neuron wiring prior to stroke (top) and rewiring after at least 1 month of recovery (bottom). Prior to stroke, strong segregation between hindlimb and forelimb maps at the level of individual neurons is observed. Within these relatively selective maps, some neurons are driven by subthreshold inputs (diagonal green and red lines from other sensory territories) that are not detected using calcium imaging that reflects neuronal spiking. Although out-of-territory inputs are present, they are inhibited by interneurons resulting in potentially latent forelimb- or hindlimb-responsive neurons which are illustrated as "masked." One month after stroke, functional borders between forelimb and hindlimb maps at the level of individual neurons are blurred, and many yellow neurons with overlapping cFL and cHL responses are observed. The activation of these neurons could be through axonal sprouting/synaptogenesis, loss of interneuron activity, or other means of potentiated excitatory synaptic transmission. Enhanced responses at the level of individual neurons facilitate the remapping process.
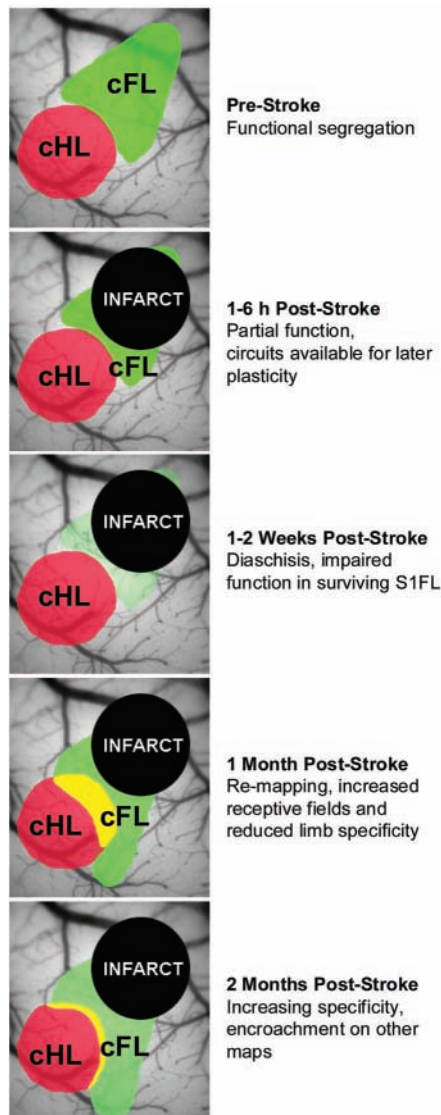
Figure 7. Summary time course of events associated with regional remapping of contralateral forelimb sensory maps after stroke. Top panel: Normal contralateral forelimb- (green map) and contralateral hindlimb-stimulated sensory maps (red map) exhibiting sharp boundaries between territories. Bottom panels: Approximate time points indicated; all maps are renderings made for illustration. Within the first 1 to 6 hours after stroke targeted to the cFL area, all activity within the infarct ceases; however, some residual cFL-stimulated activity may be present due to some sparing of local blood supply (Zhang and Murphy 2007). One to 2 weeks after stroke, little forelimb response is detected, possibly due to factors that block local activity inducing diaschisis (where apparent stroke damage at one site interferes with activity elsewhere) (Winship and Murphy 2008; Brown and others 2009). At this time point, the relatively unaffected HL area is still relatively selective for cHL stimulation. One month after stroke, remapping begins where some of the original surviving cFL and part of the cHL map begin to exhibit widened receptive fields to the point where single neurons process sensory stimuli from multiple limbs (illustrated as yellow color for neurons responding to cFL and cHL). Based on published data, the other 2 limbs would also elicit responses in the yellow region (Winship and Murphy 2008). Two months after stroke induction, some of the neurons within the original cHL map become relatively selective for cFL responses, and the overlapping yellow region is reduced in size.

and others 2007; Sato and others 2007). Axonal sprouting (Stroemer and others 1995; Li and others 1998; Carmichael and Chesselet 2002), synaptogenesis (Brown and others 2007, 2009), and cortical hyperexcitability (Domann and others 1993; Buchkremer-Ratzmann and others 1996; Schiene and others 1996; Mittman and others 1998; Neumann-Haefelin 1998; Redecker and others 2002) may potentiate these subthreshold inputs after stroke. New synapses formed via sprouting of regenerating intracortical axons from surviving neurons in the peri-infarct primary somatosensory cortex, ipsilesional secondary somatosensory areas, or contralateral primary somatosensory areas would all facilitate anatomical rewiring (Fig. 6). Similarly, reduced inhibition and increased glutamate transmission would strengthen neurotransmission at previously masked synapses or nascent synapses. Additionally, potentiation of existing subthreshold postsynaptic potentials might also give rise to more broadly tuned suprathreshold receptive fields (reduced limb selectivity), accounting for the signals observed by calcium imaging (Winship and Murphy 2008).

Functional Consequences of Reduced Limb Selectivity in Remapping

Using regional and single cell in vivo imaging (Winship and Murphy 2008), we show that individual surviving neurons are remarkably plastic and can process multiple streams of sensory information after stroke. However, this wider repertoire of neuronal processing does not preclude neurons from performing their normal duties, and over time, neurons within the heart of a reorganized territory return to a preferred stimulus (Figs. 4I-J and 7). One remaining question is the contribution of altered limb selectivity to recovery. It is conceivable that neurons responding to multiple limbs reflect a transitory phase in the progression from involvement in one sensorimotor function to a new function (replacing processing lost due to stroke). Inputs from seemingly irrelevant limbs (relative to the area damaged) may also provide background activity (Waters and Helmchen 2006) useful during plasticity in reorganized representations or may be a by-product of extensive axonal sprouting and hyperexcitability (Carmichael 2003). If reduced selectivity near the S1FL/S1HL border reflects a transition from predominantly hindlimb-associated sensation to forelimb sensorimotor function, regions of the somatosensory cortex posterior to S1FL and lateral to S1HL associated with shoulder and trunk sensation in control animals may exhibit similar altered selectivity after targeted S1FL stroke. Indeed, clinical data have shown that 50% to 85% of human stroke patients display deficits in the ability to accurately detect and discriminate tactile stimuli (Blennerhassett and others 2007; Kim

and Choi-Kwon 1996). While we did not assess sensory-evoked responses to shoulder, neck, or trunk stimulation in these regions, one might predict the same pattern of reduced stimulus selectivity as S1FL reorganization proceeds 1 to 2 months after stroke. The functional consequences of reduced selectivity and reorganization of the forelimb cortex after stroke remain to be investigated, but it is possible that reorganization of S1FL may facilitate recovery of forelimb function at the expense of hindlimb sensorimotor behaviors or trunk somatosensation.

Is Rewiring of a Subset of Neurons Significant?

Recent studies have demonstrated that small subsets of somatosensory neurons are capable of influencing animal behavior. Huber and others (2008) introduced light-gated channels into small subsets of layer 2/3 neurons in the barrel cortex of mice and demonstrated that eliciting action potentials in 60 to 300 neurons was sufficient to influence perceptual decisions. Similarly, Houwel-ing and Brecht (2008) demonstrated that juxtacellular stimulation of single somatosensory neurons affected performance in a detection task. These results suggest that the neural code for somatosensation is sparse, and small subsets of neurons may have considerable impact on sensation and behavior. Given models suggesting sparse somatosensory coding, even a small subset of functionally rewired neurons may have considerable influence on behavior during recovery.

How Are Sensory Signals Preserved despite Stroke Damage?

One question concerning remapped areas is how sensory signals are relayed if the sites of their initial thalamic inputs to the cortex are lost. The first explanation would be partial preservation of the original limb-specific sensory maps, which has been observed in acute stroke studies (Zhang and Murphy 2007) (Fig. 3C). A partial sparing of circuitry from stroke damage can extend to individual neurons as histological examination revealed that stroke-induced loss of dendritic spines can be restricted to select dendrites of even a single neuron (Enright and others 2007) (Fig. 1B-C). A second mechanism for maintenance of function would be novel cortical connections that form either as new axonal projections or were always present but previously latent. These connections could reroute sensory signals to remapping territories. Possible routes include forelimb-specific sensory signals that are sent via the ipsilateral (to stimulus) thalamus (Tommerdahl and others 2006) or the secondary somatosensory cortex (Darian-Smith and Gilbert 1995). The use of these potentially indirect signals

could explain the relatively slow time course of remapped sensory-induced depolarization reported in recent voltage-sensitive dye studies (Brown and others 2009).

A Model for Recovery after Stroke Damage

We propose a model where the spatial extent of initial stroke damage and the degree to which subthreshold sensory signals are diffusely routed determine which tissues and circuits are available to form new maps in the recovering brain (Figs. 6 and 7). It is conceivable that in regions with partial map function, restoration of function through compensatory rewiring over days to weeks may be facilitated because some of the original thalamic and intracortical connections are still present (Zhang and Murphy 2007). VSD imaging reveals a surprising degree of subthreshold intracortical connectivity between related regions of the cortex, such as sensory and motor areas, over tens of milliseconds (Berger and others 2007; Brown and others 2009; Petersen and others 2003). Conceivably, these relatively diffuse routes of sensory signaling could be strengthened over the days, weeks, and months over which recovery from stroke damage occurs (Butefisch and others 2003; Carmichael 2003; Di Filippo and others 2008; Nudo and Milliken 1996). After relatively small strokes, we suggest that within the first 24 hours (Zhang and Murphy 2007), the mammalian brain initially relies on some preserved connections from afferent sensory pathways to route signals despite injured components of sensory maps. Although this preservation of signaling apparently takes place within the first hours after stroke in the forelimb area, preliminary data from our laboratory indicate that 1 week later, the somatosensory cortex has little detectable response to contralateral forelimb stimulation (data not shown; see model in Fig. 7). It is conceivable that over a week's time, factors such as inflammation (Block and others 2005; Hossmann 1994; Jones and others 1981) and by-products of ongoing cell death (within the core) limit sensory-evoked activation through spared circuits. Two weeks after stroke, we observe somatosensory stimulation-evoked responses within individual layer 2/3 neurons near affected forelimb territories in peri-infarct S1HL (Winship and Murphy 2008). At this time after stroke, the responses were still relatively limb selective (for the cHL), similar to the patterns observed within the first 24 hours after stroke, and presumably involved intact circuits that were spared from damage. One month after stroke, we observed clear signs of plasticity as the response selectivity of individual neurons was altered, with some layer 2/3 neurons in the remapped cortex responding to stimulation of all 4 limbs. This functional rewiring could be facilitated by increased growth-associated gene expression and the resulting axonal sprouting and synaptogenesis that occur

during the first month after stroke (Brown and others 2009; Brown and others 2007; Brown and Murphy 2008; Carmichael and Chesselet 2002; Li and Carmichael 2006; Stroemer and others 1995) (Fig. 6). As active remapping evolves during stroke recovery, neurons become more selective and exhibit a preferred sensory modality (e.g., cFL- or cHL-selective) (Winship and Murphy 2008). In summary, we propose that remapping of function is accomplished both through the opportunistic use of residual surviving circuitry and plasticity in new axonal and dendritic circuits.

Future Directions

Here, we describe events associated with the reorganization of cortical structure and function after stroke. Remaining challenges for the field will be to unambiguously link these changes to improved behavioral function of recovering animals. Recent evidence from transient inactivation studies has implicated the undamaged hemisphere in behavioral recovery after large strokes (Biernaskie and others 2005). While informative, inactivation studies such as these do not implicate specific circuits and may lack the resolution to selectively target the peri-infarct region. To interrogate the effect of specific circuits, new genetically targeted tools such as light-sensitive activators and inhibitors of neuronal function could be applied to the question of stroke recovery (Boyden and others 2005; Huber and others 2008). Currently, we are developing such tools to assay the sensorimotor system in vivo using a channel rhodopsin-2 transgenic mouse and report high-resolution automated motor mapping (Ayling and others 2009). Conceivably, this optical mapping approach could be extended to produce patterned stimulation or inhibition of the peri-infarct or contralesional hemisphere, or even used to restore function as recently shown in other systems (Alilain and others 2008; Lagali and others 2008).

Many of the new imaging and optical stimulation approaches involve the use of transgenic mice. Mice traditionally have been more difficult to use in assays of sensorimotor function than rats or higher species. Furthermore, existing behavioral assays are potentially difficult to relate to simple circuits. An area for improvement is in the generation of more simplistic and quantitative sensorimotor assays that can be performed concurrently with high-resolution electrophysiological or imaging investigations in rodent models. Recently, the field of human motor function has been aided through the use of transcranial magnetic stimulation paradigms to assay specific excitatory and inhibitory cortical circuits (Hallett 2007). It is conceivable that similar paradigms using more focused methods of brain activation or inhibition could be applied to the problem of recovering networks after stroke to determine the relative contributions of select excitatory and inhibitory networks. In summary, we feel that much has been learned about the cellular and circuit level changes that occur following stroke-induced damage. The next challenge will be to apply this information to rehabilitative strategies employed on patients that lead to improved functional outcome (Boyd and Winstein 2003). Implementation of novel circuit-level therapeutic strategies will require novel paradigms of rehabilitation or skilled training as recently put into practice by some investigators (Ploughman and Corbett 2004) and perhaps aided by new insights and rules derived from animal studies.

References

Abo M, Chen Z, Lai LJ, Reese T, Bjelke B. 2001. Functional recovery after brain lesion–contralateral neuromodulation: an fMRI study. Neuroreport 12(7):1543–7.

Alilain WJ, Li X, Horn KP, Dhingra R, Dick TE, Herlitze S, and others. 2008. Light-induced rescue of breathing after spinal cord injury. J Neurosci 28(46):11862–870.

Ayling O, Harrison TC, Boyd JD, Goroshkov A, Murphy TH. 2009. Automated light based mapping of motor cortex by activation of channelrhodopsin-2 transgenic mice. Nature Methods 6(3):219–24.

Berger T, Borgdorff A, Crochet S, Neubauer FB, Lefort S, Fauvet B, and others. 2007. Combined voltage and calcium epifluorescence imaging in vitro and in vivo reveals subthreshold and suprathreshold dynamics of mouse barrel cortex. J Neurophysiol 97(5):3751–62.

Biernaskie J, Chernenko G, Corbett D. 2004. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. J Neurosci 24(5):1245–54.

Biernaskie J, Corbett D. 2001. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. J Neurosci 21(14):5272–80.

Biernaskie J, Szymanska A, Windle V, Corbett D. 2005. Bi-hemispheric contribution to functional motor recovery of the affected forelimb following focal ischemic brain injury in rats. Eur J Neurosci 21(4):989–99.

Blennerhassett JM, Matyas TA, Carey LM. 2007. Impaired discrimination of surface friction contributes to pinch grip deficit after stroke. Neurorehabil Neural Repair 21(3):263–72.

Block F, Dihne M, Loos M. 2005. Inflammation in areas of remote changes following focal brain lesion. Prog Neurobiol 75(5):342–65.

Bonhoeffer T, Grinvald A. 1996. Optical imaging based on intrinsic signals: the methodology. In: Toga AW, Mazziotta JC, editors. Brain mapping: the methods. San Diego (CA): Academic Press. p 55–97.

Boyd LA, Winstein CJ. 2003. Impact of explicit information on implicit motor-sequence learning following middle cerebral artery stroke. Phys Ther 83(11):976–89.

Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. 2005. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci 8(9): 1263–8.

Brecht M, Fee MS, Garaschuk O, Helmchen F, Margrie TW, Svoboda K, Osten P. 2004. Novel approaches to monitor and manipulate single neurons in vivo. J Neurosci 24(42):9223–7.

Brown CE, Aminoltejari K, Erb H, Winship IR, Murphy TH. 2009. 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 29(6):1719-734.

Brown CE, Li P, Boyd JD, Delaney KR, Murphy TH. 2007. Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. J Neurosci 27(15):4101–9.

Brown CE, Murphy TH. 2008. Livin' on the edge: imaging dendritic spine turnover in the peri-infarct zone during ischemic stroke and recovery. Neuroscientist 14(2):139–46.

Brown CE, Wong C, Murphy TH. 2008. Rapid morphologic plasticity of peri-infarct dendritic spines after focal ischemic stroke. Stroke 39(4):1286–91.

Buchkremer-Ratzmann I, August M, Hagemann G, Witte OW. 1996. Electrophysiological transcortical diaschisis after cortical photothrombosis in rat brain. Stroke 27(6):1105–9, discussion 1109–11.

Buonomano DV, Merzenich MM. 1998. Cortical plasticity: from synapses to maps. Annu Rev Neurosci 21:149–86.

Butefisch CM, Netz J, Wessling M, Seitz RJ, Homberg V. 2003. Remote changes in cortical excitability after stroke. Brain 126(Pt 2):470–81.

Calautti C, Baron JC. 2003. Functional neuroimaging studies of motor recovery after stroke in adults: a review. Stroke 34(6):1553–66.

Carey JR, Kimberley TJ, Lewis SM, Auerbach EJ, Dorsey L, Rundquist P, Ugurbil K. 2002. Analysis of fMRI and finger tracking training in subjects with chronic stroke. Brain 125(Pt 4):773–88.

Carmichael ST. 2003. Plasticity of cortical projections after stroke. Neuroscientist 9(1):64–75.

Carmichael ST. 2006. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann Neurol 59(5):735–42.

Carmichael ST, Chesselet MF. 2002. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. J Neurosci 22(14):6062–70.

Carmichael ST, Wei L, Rovainen CM, Woolsey TA. 2001. New patterns of intracortical projections after focal cortical stroke. Neurobiol Dis 8(5):910–22.

Castro-Alamancos MA, Borrel J. 1995. Functional recovery of forelimb response capacity after forelimb primary motor cortex damage in the rat is due to the reorganization of adjacent areas of cortex. Neuroscience 68(3):793–805.

Centonze D, Rossi S, Tortiglione A, Picconi B, Prosperetti C, De Chiara V, and others. 2007. Synaptic plasticity during recovery from permanent occlusion of the middle cerebral artery. Neurobiol Dis 27(1):44–53.

Chollet F, DiPiero V, Wise RJ, Brooks DJ, Dolan RJ, Frackowiak RS. 1991. The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. Ann Neurol 29(1):63–71.

Cicinelli P, Traversa R, Rossini PM. 1997. Post-stroke reorganization of brain motor output to the hand: a 2-4 month follow-up with focal magnetic transcranial stimulation. Electroencephalogr Clin Neurophysiol 105(6):438–50.

Coq JO, Xerri C. 1999. Acute reorganization of the forepaw representation in the rat SI cortex after focal cortical injury: neuroprotective effects of piracetam treatment. Eur J Neurosci 11(8):2597–608.

Cramer SC, Bastings EP. 2000. Mapping clinically relevant plasticity after stroke. Neuropharmacology 39(5):842–51.

Cramer SC, Nelles G, Benson RR, Kaplan JD, Parker RA, Kwong KK, and others. 1997. A functional MRI study of subjects recovered from hemiparetic stroke. Stroke 28(12):2518–27.

Dancause N, Barbay S, Frost SB, Plautz EJ, Chen D, Zoubina EV, and others. 2005. Extensive cortical rewiring after brain injury. J Neurosci 25(44):10167–79.

Darian-Smith C, Gilbert CD. 1995. Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. J Neurosci 15(3 Pt 1):1631–47.

Devor A, Dunn AK, Andermann ML, Ulbert I, Boas DA, Dale AM. 2003. Coupling of total hemoglobin concentration, oxygenation, and neural activity in rat somatosensory cortex. Neuron 39(2):353–9.

Di Filippo M, Sarchielli P, Picconi B, Calabresi P. 2008. Neuroinflammation and synaptic plasticity: theoretical basis for a novel, immune-centred, therapeutic approach to neurological disorders. Trends Pharmacol Sci 29(8):402–12.

Dijkhuizen RM, Ren J, Mandeville JB, Wu O, Ozdag FM, Moskowitz MA, and others. 2001. Functional magnetic resonance imaging of reorganization in rat brain after stroke. Proc Natl Acad Sci U S A 98(22):12766–71.

Dijkhuizen RM, Singhal AB, Mandeville JB, Wu O, Halpern EF, Finklestein SP, and others. 2003. Correlation between brain reorganization, ischemic damage, and neurologic status after transient focal cerebral ischemia in rats: a functional magnetic resonance imaging study. J Neurosci 23(2):510–7.

Domann R, Hagemann G, Kraemer M, Freund HJ, Witte OW. 1993. Electrophysiological changes in the surrounding brain tissue of photochemically induced cortical infarcts in the rat. Neurosci Lett 155(1):69–72.

Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank DW. 2007. Imaging large-scale neural activity with cellular resolution in awake, mobile mice. Neuron 56(1):43–57.

Dragoi V, Turcu CM, Sur M. 2001. Stability of cortical responses and the statistics of natural scenes. Neuron 32(6):1181–92.

Enright LE, Zhang S, Murphy TH. 2007. Fine mapping of the spatial relationship between acute ischemia and dendritic structure indicates selective vulnerability of layer V neuron dendritic tufts within single neurons in vivo. J Cereb Blood Flow Metab 27:1185–1200.

Eysel UT, Schweigart G. 1999. Increased receptive field size in the surround of chronic lesions in the adult cat visual cortex. Cereb Cortex 9(2):101–9.

Ferezou I, Haiss F, Gentet LJ, Aronoff R, Weber B, Petersen CC. 2007. Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. Neuron 56(5):907–23.

Fridman EA, Hanakawa T, Chung M, Hummel F, Leiguarda RC, Cohen LG. 2004. Reorganization of the human

ipsilesional premotor cortex after stroke. Brain 127 (Pt 4):747–58.

Friel KM, Heddings AA, Nudo RJ. 2000. Effects of postlesion experience on behavioral recovery and neurophysiologic reorganization after cortical injury in primates. Neurorehabil Neural Repair 14(3):187–98.

Frost SB, Barbay S, Friel KM, Plautz EJ, Nudo RJ. 2003. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. J Neurophysiol 89(6):3205–14.

Frostig RD, Lieke EE, Ts'o DY, Grinvald A. 1990. Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-resolution optical imaging of intrinsic signals. Proc Natl Acad Sci U S A 87(16):6082–6.

Gharbawie OA, Gonzalez CL, Williams PT, Kleim JA, Whishaw IQ. 2005. Middle cerebral artery (MCA) stroke produces dysfunction in adjacent motor cortex as detected by intracortical microstimulation in rats. Neuroscience 130(3):601–10.

Gilbert CD. 1998. Adult cortical dynamics. Physiol Rev 78(2):467–85.

Gonzalez CL, Kolb B. 2003. A comparison of different models of stroke on behaviour and brain morphology. Eur J Neurosci 18(7):1950–62.

Grinvald A, Lieke E, Frostig RD, Gilbert CD, Wiesel TN. 1986. Functional architecture of cortex revealed by optical imaging of intrinsic signals. Nature 324(6095):361–4.

Grutzendler J, Kasthuri N, Gan WB. 2002. Long-term dendritic spine stability in the adult cortex. Nature 420(6917): 812–6.

Hagemann G, Redecker C, Neumann-Haefelin T, Freund HJ, Witte OW. 1998. Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. Ann Neurol 44(2):255–8.

Hallett M. 2007. Transcranial magnetic stimulation: a primer. Neuron 55(2):187–99.

Herholz K, Heiss WD. 2000. Functional imaging correlates of recovery after stroke in humans. J Cereb Blood Flow Metab 20(12):1619–31.

Holtmaat AJ, Trachtenberg JT, Wilbrecht L, Shepherd GM, Zhang X, Knott GW, Svoboda K. 2005. Transient and persistent dendritic spines in the neocortex in vivo. Neuron 45(2):279–91.

Hossmann KA. 1994. Viability thresholds and the penumbra of focal ischemia. Ann Neurol 36(4):557–65.

Hossmann KA. 2006. Pathophysiology and therapy of experimental stroke. Cell Mol Neurobiol 26(7–8):1057–83.

Houweling AR, Brecht M. 2008. Behavioural report of single neuron stimulation in somatosensory cortex. Nature 451(7174):65–8.

Huber D, Petreanu L, Ghitani N, Ranade S, Hromadka T, Mainen Z, Svoboda K. 2008. Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice. Nature 451(7174):61–4.

Jaillard A, Martin CD, Garambois K, Lebas JF, Hommel M. 2005. Vicarious function within the human primary motor cortex? A longitudinal fMRI stroke study. Brain 128(Pt 5):1122–38.

Jenkins WM, Merzenich MM. 1987. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. Prog Brain Res 71:249–66.

Johansen-Berg H, Dawes H, Guy C, Smith SM, Wade DT, Matthews PM. 2002a. Correlation between motor improvements and altered fMRI activity after rehabilitative therapy. Brain 125(Pt 12):2731–42.

Johansen-Berg H, Rushworth MF, Bogdanovic MD, Kischka U, Wimalaratna S, Matthews PM. 2002b. The role of ipsilateral premotor cortex in hand movement after stroke. Proc Natl Acad Sci U S A 99(22):14518–23.

Jones TH, Morawetz RB, Crowell RM, Marcoux FW, FitzGibbon SJ, DeGirolami U, Ojemann RG. 1981. Thresholds of focal cerebral ischemia in awake monkeys. J Neurosurg 54(6):773–82.

Kerr JN, Denk W. 2008. Imaging in vivo: watching the brain in action. Nat Rev Neurosci 9(3):195–205.

Kerr JN, Greenberg D, Helmchen F. 2005. Imaging input and output of neocortical networks in vivo. Proc Natl Acad Sci U S A 102(39):14063–8.

Kim JS, Choi-Kwon S. 1996. Discriminative sensory dysfunction after unilateral stroke. Stroke 27(4):677–82.

Kleim JA, Bruneau R, VandenBerg P, MacDonald E, Mulrooney R, Pocock D. 2003. Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. Neurol Res 25(8):789–93.

Lagali PS, Balya D, Awatramani GB, Munch TA, Kim DS, Busskamp V, and others. 2008. Light-activated channels targeted to ON bipolar cells restore visual function in retinal degeneration. Nat Neurosci 11(6):667–75.

Li P, Murphy TH. 2008. Two-photon imaging during prolonged middle cerebral artery occlusion in mice reveals recovery of dendritic structure after reperfusion. J Neurosci 28(46):11970–9.

Li S, Carmichael ST. 2006. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. Neurobiol Dis 23(2):362–73.

Li Y, Jiang N, Powers C, Chopp M. 1998. Neuronal damage and plasticity identified by microtubule-associated protein 2, growth-associated protein 43, and cyclin D1 immunoreactivity after focal cerebral ischemia in rats. Stroke 29(9):1972–80, discussion 1980–1.

Liepert J, Bauder H, Wolfgang HR, Miltner WH, Taub E, Weiller C. 2000. Treatment-induced cortical reorganization after stroke in humans. Stroke 31(6):1210–6.

Liepert J, Miltner WH, Bauder H, Sommer M, Dettmers C, Taub E, Weiller C. 1998. Motor cortex plasticity during constraint-induced movement therapy in stroke patients. Neurosci Lett 250(1):5–8.

Manganotti P, Acler M, Zanette GP, Smania N, Fiaschi A. 2008. Motor cortical disinhibition during early and late recovery after stroke. Neurorehabil Neural Repair 22(4): 396–403.

Mao T, O'Connor DH, Scheuss V, Nakai J, Svoboda K. 2008. Characterization and subcellular targeting of GCaMP-type genetically-encoded calcium indicators. PLoS ONE 3(3):e1796.

Mittmann T, Qu M, Zilles K, Luhmann HJ. 1998. Long-term cellular dysfunction after focal cerebral ischemia: in vitro analyses. Neuroscience 85(1):15–27.

Mrsic-Flogel TD, Hofer SB, Ohki K, Reid RC, Bonhoeffer T, Hubener M. 2007. Homeostatic regulation of eye-specific

responses in visual cortex during ocular dominance plasticity. Neuron 54(6):961–72.

Murphy TH, Li P, Betts K, Liu R. 2008. Two-photon imaging of stroke onset in vivo reveals that NMDA-receptor independent ischemic depolarization is the major cause of rapid reversible damage to dendrites and spines. J Neurosci 28(7):1756–72.

Nagayama S, Zeng S, Xiong W, Fletcher ML, Masurkar AV, Davis DJ, and others. 2007. In vivo simultaneous tracing and ca(2+) imaging of local neuronal circuits. Neuron 53(6):789–803.

Nelles G, Spiekermann G, Jueptner M, Leonhardt G, Muller S, Gerhard H, Diener HC. 1999a. Reorganization of sensory and motor systems in hemiplegic stroke patients: a positron emission tomography study. Stroke 30(8):1510–6.

Nelles G, Spiekermann G, Jueptner M, Leonhardt G, Muller S, Gerhard H, Diener HC. 1999b. Evolution of functional reorganization in hemiplegic stroke: a serial positron emission tomographic activation study. Ann Neurol 46(6):901–9.

Neumann-Haefelin T, Staiger JF, Redecker C, Zilles K, Fritschy JM, Mohler H, Witte OW. 1998. Immunohistochemical evidence for dysregulation of the GABAergic system ipsilateral to photochemically induced cortical infarcts in rats. Neuroscience 87(4):871–9.

Nudo RJ, Milliken GW. 1996. Reorganization of movement representations in primary motor cortex following focal ischemic infarcts in adult squirrel monkeys. J Neurophysiol 75(5):2144–9.

Ohki K, Chung S, Ch'ng YH, Kara P, Reid RC. 2005. Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. Nature 433(7026): 597–603.

Ohki K, Chung S, Kara P, Hubener M, Bonhoeffer T, Reid RC. 2006. Highly ordered arrangement of single neurons in orientation pinwheels. Nature 442(7105):925–8.

Petersen CC, Grinvald A, Sakmann B. 2003. Spatiotemporal dynamics of sensory responses in layer 2/3 of rat barrel cortex measured in vivo by voltage-sensitive dye imaging combined with whole-cell voltage recordings and neuron reconstructions. J Neurosci 23(4):1298–309.

Ploughman M, Corbett D. 2004. Can forced-use therapy be clinically applied after stroke? An exploratory randomized controlled trial. Arch Phys Med Rehabil 85(9):1417–23.

Redecker C, Wang W, Fritschy JM, Witte OW. 2002. Widespread and long-lasting alterations in GABA(A)-receptor subtypes after focal cortical infarcts in rats: mediation by NMDA-dependent processes. J Cereb Blood Flow Metab 22(12):1463–75.

Reinecke S, Dinse HR, Reinke H, Witte OW. 2003. Induction of bilateral plasticity in sensory cortical maps by small unilateral cortical infarcts in rats. Eur J Neurosci 17(3):623–7.

Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA. 2001. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. Behav Brain Res 123(2):133–41.

Rochefort NL, Jia H, Konnerth A. 2008. Calcium imaging in the living brain: prospects for molecular medicine. Trends Mol Med 14(9):389–99.

Rossini PM. 2001. Tracking post-stroke recovery with magnetoencephalography. Ann Neurol 49(1):136.

Rossini PM, Altamura C, Ferreri F, Melgari JM, Tecchio F, Tombini M, and others. 2007. Neuroimaging experimental studies on brain plasticity in recovery from stroke. Eura Medicophys 43(2):241–54.

Rossini PM, Caltagirone C, Castriota-Scanderbeg A, Cicinelli P, Del Gratta C, Demartin M, and others. 1998. Hand motor cortical area reorganization in stroke: a study with fMRI, MEG and TCS maps. Neuroreport 9(9):2141–6.

Rouiller EM, Yu XH, Moret V, Tempini A, Wiesendanger M, Liang F. 1998. Dexterity in adult monkeys following early lesion of the motor cortical hand area: the role of cortex adjacent to the lesion. Eur J Neurosci 10(2):729–40.

Sato TR, Gray NW, Mainen ZF, Svoboda K. 2007. The functional microarchitecture of the mouse barrel cortex. PLoS Biol 5(7):e189.

Schaechter JD. 2004. Motor rehabilitation and brain plasticity after hemiparetic stroke. Prog Neurobiol 73(1):61–72.

Schaechter JD, Moore CI, Connell BD, Rosen BR, Dijkhuizen RM. 2006. Structural and functional plasticity in the somatosensory cortex of chronic stroke patients. Brain 129(Pt 10):2722–33.

Schiene K, Bruehl C, Zilles K, Qu M, Hagemann G, Kraemer M, Witte OW. 1996. Neuronal hyperexcitability and reduction of GABAA-receptor expression in the surround of cerebral photothrombosis. J Cereb Blood Flow Metab 16(5):906–14.

Schummers J, Marino J, Sur M. 2002. Synaptic integration by V1 neurons depends on location within the orientation map. Neuron 36(5):969–78.

Schummers J, Yu H, Sur M. 2008. Tuned responses of astrocytes and their influence on hemodynamic signals in the visual cortex. Science 320(5883):1638–43.

Schweigart G, Eysel UT. 2002. Activity-dependent receptive field changes in the surround of adult cat visual cortex lesions. Eur J Neurosci 15(10):1585–96.

Seitz RJ, Hoflich P, Binkofski F, Tellmann L, Herzog H, Freund HJ. 1998. Role of the premotor cortex in recovery from middle cerebral artery infarction. Arch Neurol 55(8):1081–8.

Stosiek C, Garaschuk O, Holthoff K, Konnerth A. 2003. In vivo two-photon calcium imaging of neuronal networks. Proc Natl Acad Sci U S A 100(12):7319–24.

Stroemer RP, Kent TA, Hulsebosch CE. 1995. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke 26(11): 2135–44.

Tommerdahl M, Simons SB, Chiu JS, Favorov O, Whitsel BL. 2006. Ipsilateral input modifies the primary somatosensory cortex response to contralateral skin flutter. J Neurosci 26(22):5970–7.

Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. 2002. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420(6917):788–94.

Traversa R, Cicinelli P, Bassi A, Rossini PM, Bernardi G. 1997. Mapping of motor cortical reorganization after stroke: a brain stimulation study with focal magnetic pulses. Stroke 28(1):110–7.

van der Zijden JP, van der Toorn A, van der Marel K, Dijkhuizen RM. 2008. Longitudinal in vivo MRI of alterations in perilesional tissue after transient ischemic stroke in rats. Exp Neurol 212(1):207–12.

van der Zijden JP, Wu O, van der Toorn A, Roeling TP, Bleys RL, Dijkhuizen RM. 2007. Changes in neuronal connectivity after stroke in rats as studied by serial manganese-enhanced MRI. Neuroimage 34(4):1650–7.

Wang X, Lou N, Xu Q, Tian GF, Peng WG, Han X, and others. 2006. Astrocytic Ca2+ signaling evoked by sensory stimulation in vivo. Nat Neurosci 9(6):816–23.

Ward NS, Brown MM, Thompson AJ, Frackowiak RS. 2003a. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. Brain 126(Pt 11):2476–96.

Ward NS, Brown MM, Thompson AJ, Frackowiak RS. 2003b. Neural correlates of outcome after stroke: a cross-sectional fMRI study. Brain 126(Pt 6):1430–48.

Ward NS, Brown MM, Thompson AJ, Frackowiak RS. 2006. Longitudinal changes in cerebral response to proprioceptive input in individual patients after stroke: an FMRI study. Neurorehabil Neural Repair 20(3):398–405.

Waters J, Helmchen F. 2006. Background synaptic activity is sparse in neocortex. J Neurosci 26(32):8267–77.

Watson BD, Dietrich WD, Busto R, Wachtel MS, Ginsberg MD. 1985. Induction of reproducible brain infarction by photochemically initiated thrombosis. Ann Neurol 17(5):497–504.

Weber R, Ramos-Cabrer P, Justicia C, Wiedermann D, Strecker C, Sprenger C, Hoehn M. 2008. Early prediction of functional recovery after experimental stroke: functional magnetic resonance imaging, electrophysiology, and behavioral testing in rats. J Neurosci 28(5):1022–9.

Wei L, Erinjeri JP, Rovainen CM, Woolsey TA. 2001. Collateral growth and angiogenesis around cortical stroke. Stroke 32(9):2179–184.

Weiller C, Ramsay SC, Wise RJ, Friston KJ, Frackowiak RS. 1993. Individual patterns of functional reorganization in the human cerebral cortex after capsular infarction. Ann Neurol 33(2):181–9.

Winship IR, Murphy TH. 2008. In vivo calcium imaging reveals functional rewiring of single somatosensory neurons after stroke. J Neurosci 28(26):6592–606.

Winship IR, Plaa N, Murphy TH. 2007. Rapid astrocyte calcium signals correlate with neuronal activity and onset of the hemodynamic response in vivo. J Neurosci 27(23):6268–72.

Zepeda A, Sengpiel F, Guagnelli MA, Vaca L, Arias C. 2004. Functional reorganization of visual cortex maps after ischemic lesions is accompanied by changes in expression of cytoskeletal proteins and NMDA and GABA(A) receptor subunits. J Neurosci 24:1812–1821.

Zepeda A, Vaca L, Arias C, Sengpiel F. 2003. Reorganization of visual cortical maps after focal ischemic lesions. J Cereb Blood Flow Metab 23:811–820.

Zhang S, Boyd J, Delaney K, Murphy TH. 2005. Rapid reversible changes in dendritic spine structure in vivo gated by the degree of ischemia. J Neurosci 25(22):5333–8.

Zhang S, Murphy TH. 2007. Imaging the impact of cortical microcirculation on synaptic structure and sensory-evoked hemodynamic responses in vivo. PLoS Biol 5(5):e119.

Zuo Y, Lin A, Chang P, Gan WB. 2005. Development of long-term dendritic spine stability in diverse regions of cerebral cortex. Neuron 46(2):181–9.