Plasticity during stroke recovery: from synapse to behaviour

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Abstract | Reductions in blood flow to the brain of sufficient duration and extent lead to stroke, which results in damage to neuronal networks and the impairment of sensation, movement or cognition. Evidence from animal models suggests that a time-limited window of neuroplasticity opens following a stroke, during which the greatest gains in recovery occur. Plasticity mechanisms include activity-dependent rewiring and synapse strengthening. The challenge for improving stroke recovery is to understand how to optimally engage and modify surviving neuronal networks, to provide new response strategies that compensate for tissue lost to injury.

Recovery
The re-emergence of the exact motor and sensory patterns that were in place before stroke. However, true recovery is rarely observed and most animal and human tests only assess performance changes, which typically are compensatory in nature.

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Interruptions in the blood supply to the brain lead to a debilitating neurological condition termed stroke[1]. Stroke is the leading cause of chronic adult disability and the third leading cause of death in North America. During a stroke, oxygen- and energy-hungry neurons that are deprived of their normal metabolic substrates cease to function in seconds and show signs of structural damage after only 2 minutes[2]. As energy-dependent processes fail, neurons are unable to maintain their normal transmembrane ionic gradients, resulting in an ion and water imbalance that leads to apoptotic and necrotic cell death cascades[1,3] and, ultimately, the impairment of sensory and motor function[1,4] (FIG. 1). Although stroke damage can be devastating, many patients survive the initial event and undergo some spontaneous recovery, which can be further augmented by rehabilitative therapy.

Experimental stroke models (BOX 1) are well developed and relatively straightforward, and the effects of stroke in these models are apparent only minutes after blood flow is reduced. This has obvious advantages over animal models of chronic neurodegenerative diseases, which in some cases take months or even years to develop phenotypes. We therefore predict a bright future for stroke research, in particular success for strategies to promote synapse and network level plasticity that leads to the recovery of function.

Here, we concentrate on the events that are associated with recovery from stroke damage and not the initial mechanisms of ion imbalance or cell death that are reviewed elsewhere[5]. We discuss recent advances in the field of stroke recovery and highlight evidence that demonstrates the remarkable capacity of the adult brain to undergo plasticity that promotes recovery from stroke damage. This topic is particularly exciting as recent data

suggest parallels between plasticity mechanisms in the developing nervous system and those taking place in the adult brain after stroke[6–11]. The hope is that by understanding the mechanisms that lead to functional recovery we could augment the naturally occurring recovery capabilities of the brain. Here, we discuss common themes between activity-dependent plasticity and recovery after stroke.

What is functional recovery?

Often, patients that have experienced a stroke exhibit continued functional recovery for many years following their initial injury[12]. Similar patterns of improved behavioural performance are also observed in animal stroke models and can be facilitated by behavioural training (FIG. 2), although the time course of post-stroke recovery is typically much shorter in animals. Clinical and biomedical scientists refer to the enhanced sensory and motor performance that occurs after stroke as recovery, although re-emergent post-stroke behaviour is unlikely to be identical to pre-stroke behavioural patterns owing to the loss of neurons that have highly specific functions. Commonly used human and animal behavioural assessment protocols (BOX 2) can rarely determine the extent to which improved performance reflects true recovery, behavioural compensation or a combination of both. Indeed, detailed post-injury kinematic analysis of the reaching movements of rats shows that impairments in the range of motion, grasping and supination of the forelimb are offset by postural adjustments (such as a change of body angle or shoulder and trunk rotations)[13] that allow a partial return to pre-stroke motor performance levels. However, true recovery, with relatively little compensation, can occur after small cortical lesions[14]
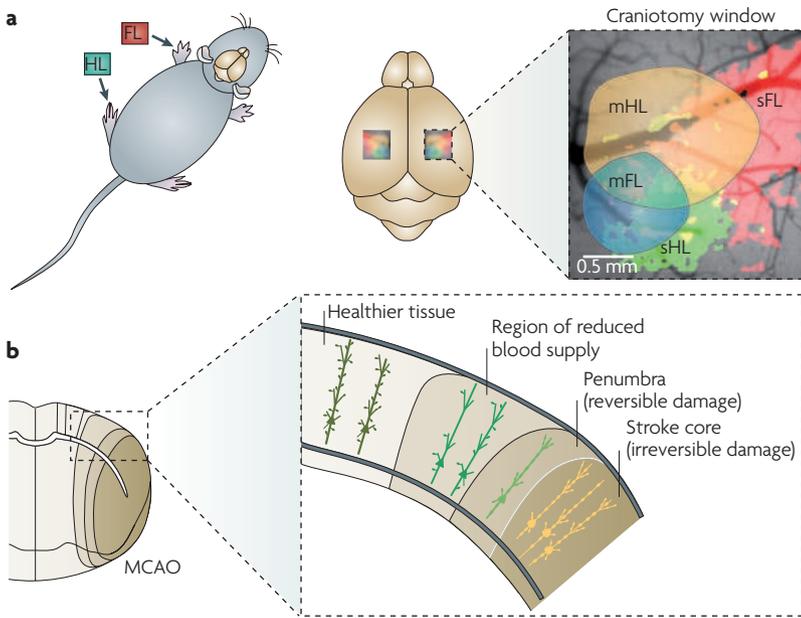
Figure 1 | **Organization of the sensorimotor cortex and the relationship between synaptic circuit damage and local blood flow. a** | Cartoon showing the location of mouse forelimb (sFL) and hindlimb (sHL) somatosensory cortex and adjacent motor cortex areas (mFL and mHL), prepared by overlaying sensory and motor functional maps on an image of the brain vasculature. Sensory pathways are typically contralateral, such that signals from the left limb go to the right cortex. However, a minority of sensory pathways are ipsilateral. **b** | Cross section through the rodent cortex that shows the stroke core (darker brown) and penumbra (lighter brown)[158] after occlusion of the middle cerebral artery, a common experimental stroke model (BOX 1). The core has less than 20% of baseline blood flow and fails to regain its fine dendritic structure after reperfusion[45]. In the penumbra, blood flow increases towards the midline, as tissues in this region are supplied by other artery systems that were not blocked during the stroke, and some loss of dendrite structure will reverse when reperfusion occurs. This is where rewiring will occur to replace connectivity that has been lost because of the stroke[45]. MCAO, middle cerebral artery occlusion. Data in part **a** are from REFS 4,131.

Plasticity
Changes in the strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network.

Behavioural compensation
The restoration of performance through the use of modified or alternative response strategies, such as relying on the unimpaired limb or incorporating postural changes (for example, shoulder and trunk rotations) to perform motor tasks.

Somatotopic
Organized by body parts, for example somatosensory cortex maps.

because some of the tissue that is crucial for function is spared. Similar kinematic analysis and electromyography recording in stroke patients during reaching and grasping indicate that similar compensatory mechanisms function after stroke[15,16]. Currently, the interest of many stroke scientists is to understand how these compensation processes bring about recovery.

The motor and sensory cortices are loosely organized into somatotopic functional maps that exhibit high levels of use-dependent plasticity — that is, the maps can be modified by experience[17]. Motor maps reflect the coupling of specific motor cortex neurons to muscles, whereas sensory maps represent the pairing of body parts to sensory cortex neurons. Motor maps enable both the learning and the expression of movements and therefore represent a type of 'motor engram' or memory trace[18]. Accordingly, when regions of cortex are destroyed by stroke the motor engram is lost. As such, the only way to achieve true recovery might be to replace the destroyed circuits[13], perhaps through further development of innovative strategies such as stem cell therapy[19–21] (BOX 3). However, whether stem cell-derived neurons can make a significant contribution to newly formed circuits in adult animals is currently unclear[22]. Given this limitation, the term recovery usually

refers to varying degrees of behavioural compensation that are provided by the remaining and newly developed brain circuits and that lead to altered behavioural patterns and/or new response strategies to improve performance[13,23–25]. In this Review, recovery is used to mean improved performance without distinguishing between the degree of compensation and pure recovery.

Factors contributing to recovery

Many of the mechanisms that underlie recovery are similar to those involved with plasticity in the intact brain[26]. Here, we expand on the premise that stroke recovery mechanisms are based on both structural and functional changes in brain circuits that have a close functional relationship to those affected by stroke (FIG. 1), and the premise that they follow similar rules to those that hold during the development of the nervous system and experience-dependent plasticity. Two related factors enable plasticity in the adult brain after stroke. First, a surprising amount of diffuse and redundant connectivity exists in the CNS and, second, new structural and functional circuits can form through remapping between related cortical regions (FIG. 3).

If there's a wire there's a way: diffuse connectivity. Typically, well-defined synaptic connectivity in the CNS is formed during development and is later sculpted by activity. However, it has been shown that the neurons that contribute to complex functions, such as a memory trace or engram, are not localized in a single brain region but are distributed throughout the cortex[27]. Therefore, despite its defined circuit structure, the brain functions as a spatially distributed computational machine that routes signals along multiple pathways, each capable of adapting to changes in transmission fidelity. This diffuse connectivity, together with redundancy in neuronal processing, might facilitate recovery from stroke damage.

Although the canonical view of sensory and motor processing is that body parts are controlled by neurons in the cerebral hemisphere on the opposite side of the body (BOX 4; FIG.1), ipsilateral pathways — in which, for example, the right hemisphere controls the right side of the body — are also present[28,29]. One way in which the human stroke-injured brain restores function is through the use of a distributed neural network involving brain regions that, in a functional hierarchy, are both upstream and downstream of the region affected by infarction[12,30,31]. These networks can include brain regions in the intact contralesional hemisphere[32] (BOX 4). The use of these contralesional regions in recovery reduces lateralized activation. However, an emerging consensus from human imaging studies is that the most successful recovery occurs in individuals that exhibit relatively normal lateralized patterns of sensory activation in the hemisphere in which the stroke has taken place, whereas patients with larger strokes, who often show bilateral cortical activation, typically have less complete recovery[12,33] (BOX 4). Bilateral activation might therefore indicate an inability of compensatory mechanisms to restore normal, predominantly lateralized sensory activation. Therefore,

Motor cortex
The area of the cortex that is dedicated to controlling muscles.

Sensory cortex
The area of the cortex that is dedicated to processing sensation from various body parts.

Motor engram
A putative memory trace for a motor action or movement.

Remapping
The transfer of incoming sensory or motor output signals from one cortical region to another. This might not necessarily involve new structural circuits.

Ipsilateral pathways
Pathways that are present in the brain hemisphere or spinal cord on the same side as the body part to which they connect.

although the redundancy of an unaffected cortex and the potential of ipsilateral pathways seem advantageous, the issues of lateralization and function are potentially complex and reflect both the degree of injury and the extent of recovery[34,35].

Even in a cortical hemisphere, sensory signals are routed over surprisingly long distances. This provides a further opportunity for diffuse connectivity to contribute to stroke recovery. Somatosensory stimuli from a specific body part are preferentially routed through the thalamus to the primary sensory areas (termed S1) that are dedicated to that body part, but can also exhibit widely divergent activation patterns[36]. In raccoons, which have well-developed digit representations, intracellular recordings showed that spikes within S1 digit subdivisions were evoked by stimulation of only their preferred digit. However, within these same areas, subthreshold potentials were generated in ~20% of neurons in response to the stimulation of other digits or body parts, which indicates diffuse inputs[37]. Voltage-sensitive dye imaging in mice revealed surprisingly widespread intracortical connectivity between related regions of the cortex, such as sensory and motor areas[7,38,39]. For example, activity triggered by whisker movement is rapidly conveyed to parts of the sensory cortex that process signals from the limbs[7,38,39]. More recent voltage-sensitive dye imaging studies in mice indicate that some 'diffuse'

forelimb-stimulated signals can be retained in parts of the cortex that process hindlimb signals despite infarction to primary forelimb sensory areas[40]. It is therefore possible that diffuse off-target signalling could be strengthened over the days, weeks and months over which recovery from stroke damage occurs[17,41,42]. Although spared diffuse connections provide a substrate for long-term stroke recovery, exactly how and whether these connections are required is still unclear.

Location, location, location: neighbouring areas remap.
The area of tissue that borders the stroke core region typically experiences reduced blood flow and is termed the penumbra[1,4] (FIG. 1). The penumbra is also defined as the region of perfusion–diffusion mismatch by MRI imaging, in which blood flow might be reduced but infarct-related diffusion signals have yet to be found[43]. *In vivo* two-photon imaging indicates that dendrites in the penumbra are damaged by stroke but can in part recover their structure during reperfusion (the restoration of blood flow)[44,45]. However, neuronal survival in the penumbra is a time-limited process and cells will die within hours or a few days without intervention (for example, by reperfusion)[46]. Surviving neurons in the peri-infarct cortex, which is situated at the border of an infarct but has sufficient blood perfusion, undergo active structural and functional remodelling after stroke and sow the seeds for recovery. Location is everything in cortical physiology: much like the demand for a vacant lot in Manhattan, if a single digit is removed in an adult animal (a form of deafferentation) the cortical territory devoted to that digit rapidly remaps to represent the intact digits that project to the neighbouring cortex[36,47–49]. These findings indicate that even in adult animals there is intense competition for available cortical map territory. The cortex remodels after both deafferentation and stroke.

After stroke, cortical remapping is both activity dependent and based on competition. Recovering peri-infarct regions that have compromised circuits compete for map territory with healthy adjacent tissues[17] (FIG. 1). This is particularly true in animal models of relatively small strokes (those that affect 5–15% of the hemisphere) that closely resemble the relative size of a survivable human stroke[7,50,51]. Therefore, recovery after a small stroke is likely to involve peri-infarct tissue that has a similar function[7]. By contrast, after a large stroke, tissue that has a similar function might be found only at more distant sites, such as the premotor cortex (for strokes that affect the primary motor cortex)[52] or regions in the contralateral hemisphere[32], where structural remodelling can occur[165]. The sequence and kinetics of the activation of peri-infarct cortical circuits after stroke have recently been revealed in mice *in vivo* using fast voltage-sensitive dye imaging[7]. Eight weeks after stroke in the forelimb sensory cortex, the surviving portion of forelimb sensory cortex actively relays enhanced sensory signals to the motor cortex, resulting in the remapping of sensory function. Interestingly, the remapped responses last notably longer in animals that have recovered from stroke than in normal controls. The longer-lived responses also showed

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Box 1 | Animal models of focal ischaemic stroke

Intraluminal suture
A coated suture is advanced into the carotid artery until it lodges at the junction of the middle cerebral artery (MCA). The damage that results from the interruption of blood flow is mainly in the striatum and cortex[136]. The suture is withdrawn after 30–120 min, which results in the reperfusion of ischaemic tissue. Occlusion durations of 90–120 min are required to achieve reproducible tissue damage and result in very large infarcts that occupy much of the hemisphere. These often include hypothalamic injury, which can complicate the interpretation of histological and behavioural outcomes owing to impaired motivation and temperature regulation. Such extensive damage is akin to a malignant infarct in humans, which is frequently fatal or untreatable[137].

Proximal or distal middle cerebral artery occlusion
The MCA is transiently occluded using microvascular clips, or permanently occluded by cauterization. Damage is restricted to the cortex if blood flow is interrupted distal to the striatal branches of the MCA, whereas occlusion proximal to these small arteries results in both striatal and cortical injury.

Middle cerebral artery embolism
A blood clot is introduced through the internal carotid to occlude the MCA[138]. This model closely resembles human ischaemic stroke. Resulting strokes tend to be much smaller than those produced using the suture model. Clots can undergo spontaneous thrombolysis, thereby causing multiple infarcts and high variability and mortality[137,139].

Endothelin 1 vasoconstriction
Endothelin 1 (ET1) produces ischaemia by constricting blood vessels. ET1 is stereotaxically injected into parenchymal regions of interest, to constrict local arterioles, or near the MCA[140,141]. Reperfusion occurs, but at a much slower rate than with the intraluminal suture model. Lesion size can be adjusted by varying the concentration or volume of ET1 to achieve reproducible injury.

Photothrombosis
A photosensitive dye is injected systemically into animals in which a section of skull has been removed or thinned[142]. The underlying cortical blood vessels are exposed to a green laser or epifluorescent light source, generating singlet oxygen species that lead to platelet activation and microvascular occlusion. This model can be used to produce small infarcts in any cortical region without invasive surgery[4,143].
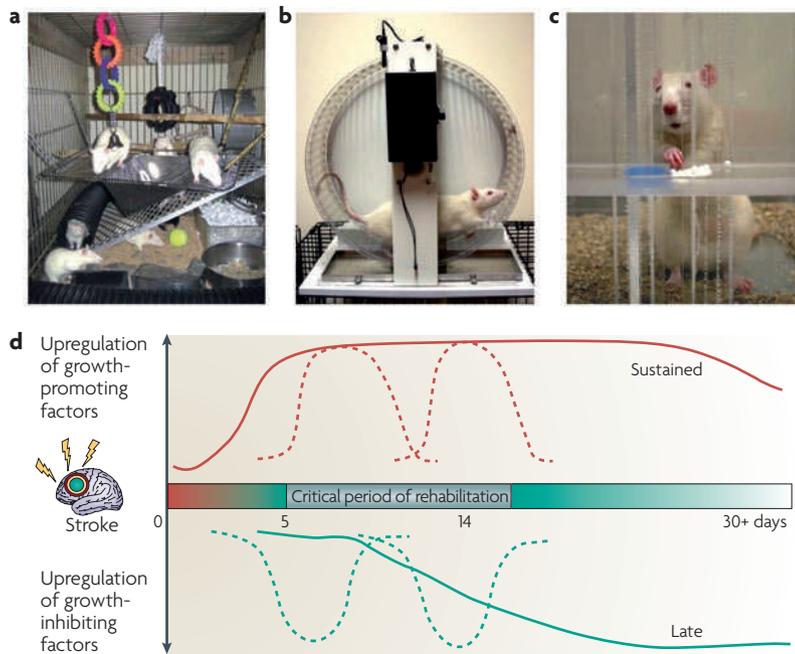
Figure 2 | **Enriched rehabilitation protocols and the critical period of post-stroke rehabilitation.** After stroke, skilled use of the affected hand (or paw) is highly resistant to recovery in both humans and animals[159,160]. In rats, enriched rehabilitation has yielded consistent and substantial improvements in the recovery of skilled reaching[6,11,102]. The protocol consists of enriched housing (**a**) and/or running exercise (**b**) in combination with several hours of daily reach training (**c**) of the impaired limb. Rats are housed in enriched environments or exposed to motorized running wheels 5–14 days after stroke. Motorized running wheel speed and running duration are gradually increased during this time. Similarly, the reach rehabilitation task is made progressively more challenging by increasing the tray height as well as the duration of the reaching session throughout rehabilitation. Running exercise immediately before the reaching session seems to have a priming effect, increasing the efficacy of the use-dependent reach training[11] (**d**). The timing of rehabilitation is designed to optimally engage neuroplasticity processes during the critical period of the early post-stroke recovery phase, during which a sustained upregulation of growth-promoting genes predominates (solid red line in part **d**). Most growth-inhibitory genes (solid green line) tend to be upregulated gradually, several weeks after stroke, towards the end of the critical period of stroke recovery. A few growth-promoting and growth-inhibiting genes are transiently upregulated (dashed lines) in the early and mid post-stroke recovery period. This critical period is observed in animal studies and might be quite different from that for human stroke, in which spontaneous recovery can extend for the first 90 days after injury[12]. Most evidence suggests that in humans earlier rehabilitation is better[76,161], but we direct readers to other work[99]. Data in part **d** are from REFS 6,9.

Infarct
The area that suffers a prolonged reduction in blood flow and undergoes sustained ischaemic depolarization during stroke. Most neurons and glia in this region will die.

Contralesional hemisphere
The hemisphere that is opposite to stroke damage. Contralateral pathways are those that are present in the brain hemisphere or spinal cord on the opposite side to a body part.

a greater degree of spreading from the motor cortex to distant cortical regions, including the retrosplenial cortex. These findings indicate that the recovery of sensorimotor functions after stroke and brain remapping involve changes in the temporal and spatial spread of sensory information processing across local and distant sites.

How the remapping of lost function is initiated, and how seemingly stroke-compromised circuits in the peri-infarct cortex can compete and win in what is thought to be an activity-dependent process, is unclear[41]. Conceivably, circuit remapping after deafferentation[36] and after stroke damage[53] involve different mechanisms, as injury-specific gene expression programmes will be engaged. The local environment might be altered after a stroke to permit residually active stroke-affected inputs to

compete more effectively for connections with intact tissues. Interestingly, the stimulation of rewiring in the peri-infarct region seems to be exclusive to stroke-affected circuits, as experience-dependent plasticity that is normally observed in healthy tissue is actually reduced in tissue 1–2 mm from the peri-infarct cortex in rat[54].

Positive factors that are induced in the peri-infarct region that might give stroke-affected circuits an edge over healthy tissues during rewiring include: glial-derived synaptogenic thrombospondin 1 and 2 (REF. 55) as well as proteins that encourage growth-related processes, including GAP43 (also known as neuromodulin), MARCKS, CAP23 (also known as BASP1) and growth factors[9,56,57]. These factors might encourage the sprouting of new axons[7,58,59] and support the increased elaboration of dendrites and spines[8,60]. Balancing these positive signals is the induced expression of negative factors that either inhibit outgrowth or repel sprouting axons, such as the extracellular matrix factors NOGO (also known as RTN4)[61–63], chondroitin sulphate proteoglycan[64], ephrin A5, semaphorin 3A and neuropilin 1, and EPH receptors and ligands[9]. The age of the animal used had an effect on the profile and timing of expression, which may be important for the translation of these findings to humans[166]. Interestingly, the induction of circuit-promoting factors tends to occur earlier than the induction of inhibitory factors after stroke[9] (FIG. 2d). These negative factors might exist to limit reorganization, ensuring that aberrant connectivity is not formed, or might simply interfere with the process. A common experimental approach to promote stroke recovery is to inhibit negative factors and to promote those that lead to process outgrowth and cell survival. For example, the administration of brain-derived neurotrophic factor (BDNF) improves recovery after stroke in rats[65], and the beneficial effects of rehabilitation on the recovery of skilled reaching are prevented in animals treated with a BDNF antisense oligonucleotide[11]. It is even conceivable that differences in plasticity mechanisms between individuals that are due to *BDNF* gene polymorphisms could result in altered levels of plasticity after stroke[66]. Insight can also be gained from studies of the factors that both negatively (for example, NOGO and chondroitin sulphate proteoglycans)[62–64] and positively (for example, SPARC)[67] regulate recovery from other forms of injury, such as spinal cord trauma. Although we have described some of the molecules implicated in the recovery process, we direct readers to other recent articles that focus more exclusively on this subject[21,68,69]. Given that the mechanisms involved in the recovery after stroke are similar to those that operate during development, it is conceivable that screens for molecules that contribute to synapse maturation might yield further permissive factors for stroke recovery[70].

Critical periods: recovery and ontogeny
The brain is highly plastic during development as new connections are formed and removed through use-dependent processes. Environmental experience during this period can markedly affect the subsequent properties and function of the adult brain. An elegant illustration of

Lateralized activation
The degree to which sensory or motor pathways are crossed, for example the degree to which the left motor cortex controls the right limb.

Representation
An area of cortex dedicated to processing a sensation from a particular body part.

Penumbra
The area that is adjacent to the infarct and contains partial blood flow. Some neurons will survive in this area. The penumbra is also defined as the region of perfusion–diffusion mismatch by MRI imaging, in which blood flow might be reduced, although infarct-related diffusion signals have not yet been found.

Deafferentation
Loss of sensory activity.

Rewiring
Changes to the structure of neuronal axons or dendrites that might affect neuronal function.

this phenomenon was provided by Hubel and Wiesel[71], who showed that visual deprivation during a 'critical period' early in life permanently alters the physiological properties of visual cortex neurons. Similar to visual cortex neurons, motor maps are initially immature and do not attain adult properties until later in life[72]. Cortical reorganization after lesion or stroke can be compared with that which occurs during normal development. For example, the recovery of feeding behaviour after bilateral lesions of the lateral hypothalamus follows the four distinct motor sequences that also characterize the development of feeding behaviour in young rats[73]. Similarly, parallels between motor recovery after stroke and the acquisition of skilled movement patterns in human infants have been noted[74]. Insights based on this analogy might have a crucial impact on the recovery of those affected by stroke, but it is important to remember that the neural circuitry of a stroke patient with a coexisting marker of morbidity (such as age or hypertension) is probably less receptive to neural remodelling than the developing brain owing to a diseased microvasculature, chronic inflammation and other plasticity-impeding processes.

Animal studies indicate that many of the genes and proteins that are important for neuronal growth, synaptogenesis and the proliferation of dendritic spines are expressed at their highest levels during early brain development and decline appreciably with ageing[75]. However, a second, limited period of increased expression of these genes is evident following stroke[9,69,74]. Thus, a critical period of heightened neuroplasticity, akin to that which occurs during visual system development, might exist after stroke (FIG. 2). If so, the implications for restoration of function are enormous because delays in initiating rehabilitation after stroke vary considerably and treatment for many patients might fall outside of this crucial time window. In one important experiment[6], rats were exposed to enriched rehabilitation (BOX 3) that started at 5, 14 or 30 days after the middle cerebral artery was occluded. The animals given early rehabilitation (5 or 14 days post-stroke) displayed significant recovery, whereas rats given delayed treatment (30 days post-stroke) exhibited little improvement. Notably, early enrichment increased the dendritic branching of layer V cortical neurons, whereas enrichment that was delayed until 30 days post-stroke had no effect. Together with recent clinical findings[76,77], these results provide strong evidence for a critical period after stroke, during which the brain is most receptive to modification by rehabilitative experience, and suggest that earlier therapy is better (FIG. 2).

Although debate continues about the optimal timing of rehabilitation, emerging evidence-based consensus studies conclude that delays to the initiation of rehabilitation are associated with a poorer outcome and a longer length of stay in hospital for patients[78,79]. Although early training is more effective, many stroke patients continue to improve long after their original injury owing to spontaneous recovery, home-based rehabilitation or as a result of constraint-induced movement therapy (BOX 3). This indicates that the time window for stroke recovery, as with that of normal learning, never really closes. However, the plastic processes that characterize early brain development and the semi-acute phase after stroke diminish and slow with time. An important challenge will be to find ways to widen this window and to keep it open for a longer period of time to optimize post-stroke recovery (Supplementary information S1 (box)). For example, digestion of extracellular chondroitin sulphate proteoglycans leads to a re-opening of visual system plasticity in adult animals[80] and the promotion of recovery after spinal cord injury[81,82]. Whether such inhibitory extracellular matrix factors will have an effect on stroke recovery is unknown.

Synaptic learning rules in recovery

The presence of critical periods and training-dependent effects suggest analogies between stroke recovery and synapse-based learning rules that are involved in both wiring and refining brain connections[83]. Assuming that the damaging effect of stroke spares some circuitry, which can route sensory signals to the brain and motor commands out of it, synapse-based learning rules could help to create compensatory circuits after stroke (FIG. 3). These learning rules can be divided into two broad conceptual classes of mechanisms: homeostatic plasticity mechanisms[84] ensure that neurons receive an adequate amount of synaptic input, and Hebbian plasticity mechanisms redistribute synaptic strength to favour the wiring of pathways that are coincidently active[85–87].

> **Box 2 | Assessment of sensory–motor recovery following stroke in animals**
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> **Neurological deficit score**
> A composite of several simple tasks, such as spontaneous ipsilateral circling, hindlimb retraction, bilateral forepaw grasping of a bar, contralateral forelimb flexion and beam walking ability[144]. The tests are graded on scales from 0–3 and added together. The test battery is fairly easy to perform but is subjective, and apparent deficits often resolve in days or weeks, depending on injury size. Caution is required when applying statistics to composite scores, as ascending rating values do not represent graded severity but instead measure different aspects of behaviour. There can be no presumption of linearity.
>
> **Skilled reaching tests**
> In the Montoya staircase test[145], mildly food-deprived animals reach to obtain food pellets from a small set of stairs that descend from either side of the platform. Forepaw dexterity can be measured by comparing the number of pellets eaten with those that are dropped or left behind. Deficits in the staircase task rarely fully recover. In the single-pellet reaching task, rodents reach through a narrow slot for a single pellet that is placed on a shelf that is attached to the front wall of the test chamber[146] (FIG. 2). A reaching success score is recorded at multiple intervals up to 8 weeks after stroke. Both tests are quantitative and sensitive to forelimb impairments. Deficits seem to be very long lasting, if not permanent[6,102].
>
> **Forelimb asymmetry test**
> Animals are placed in a small vertical cylinder that permits video recording from below. The number of contacts (either with both limbs or with the left versus the right) with the cylinder walls is noted during a 5 min test session[60]. Normally, animals use each limb equally, but following stroke there is increased reliance on the ipsilateral, or 'good', limb. Deficits resolve after several weeks.
>
> **Beam and ladder walking tasks**
> Rodents are placed on a narrow beam or ladder[147] that must be crossed to reach a darkened goal box. The motor behaviour (such as foot faults and slips) of the animal is scored. These tests are useful in detecting hindlimb and forelimb impairments in the first few weeks after stroke, after which recovery is evident.

Box 3 | Therapeutic approaches to stroke recovery

Enriched rehabilitation

Animals are housed together in large cages that contain numerous objects and shelves, which provide both sensory–motor and cognitive stimulation (FIG. 2). They are also exposed to reach training for several hours per day, during which they can obtain food rewards only by using their impaired limb[102]. This combination is more effective in restoring upper limb function after stroke than enrichment or reach training alone. Although enrichment enhances many important neuroplasticity processes, such as increased levels of brain-derived neurotrophic factor, it has yet to be incorporated into human rehabilitation approaches. However, certain elements of enrichment could be achieved by changing the physical environment (for example, by using moveable walls or changing artwork) and by providing patients with more varied activities (including greater social interaction, computer games and virtual reality).

Stem cell therapy

The idea of replacing circuits lost to stroke by promoting endogenous neurogenesis or by transplantation is very appealing[20]. However, the consensus is that the improved functional outcome after stem or progenitor cell administration is most likely due to neurotrophic effects that enhance sprouting, angiogenesis and other processes that are important in neuroplasticity and recovery[148,149], instead of differentiation into neuronal phenotypes. Questions regarding the optimal cell type, timing of transplants, route of administration, efficacy and safety concerns need to be answered before widespread clinical use of this therapy can be contemplated.

Constraint-induced movement therapy (CIMT)

This approach is derived from animal studies that show that enforcing use of the impaired limb by restraining the good forelimb results in substantial functional recovery of the impaired forelimb[150]. Human CIMT subjects wear a sling or mitten to restrict use of the good limb during waking hours for periods of several weeks. This results in lasting gains in impaired limb function months and years after stroke. CIMT is particularly beneficial in reducing counterproductive reliance on the good or unimpaired limb, a phenomenon that is termed learned non-use[151]. Indeed, learned non-use can create a condition of 'maladaptive' plasticity in which the reorganization of circuitry interferes with regaining the function of the impaired limb. The mechanisms that underlie these late functional gains are unknown, but evidence suggests that CIMT induces cortical motor map expansion[107].

Pharmacological rehabilitation

Early animal studies reported enhanced motor recovery when rehabilitation was paired with amphetamine treatment[152]. Attempts to demonstrate efficacy with amphetamine or related drugs in stroke patients and additional animal models have been disappointing[153,154]. Nonetheless, this approach continues to hold promise, especially for patients who cannot fully benefit from rehabilitation owing to physical or motivational limitations.

Homeostatic plasticity
A negative feedback-mediated form of plasticity, also known as synaptic scaling, that serves to keep network activity at a desired set point. Homeostatic plasticity might be important after stroke for setting into motion pathways that restore synaptic activity.

Hebbian plasticity
A positive feedback-mediated form of plasticity in which synapses between presynaptic and postsynaptic neurons that are coincidently active are strengthened. Hebbian plasticity might be important after stroke for strengthening and retaining properly wired connections.

Homeostatic plasticity. In homeostatic plasticity, attenuation of synaptic activity results in an upregulation of both the presynaptic release of and the postsynaptic response to neurotransmitters in an attempt to restore activity to a set point[84]. Homeostatic plasticity can be observed at nearly every synapse that has been examined, including those from isolated cultured hippocampal neurons, the *Drosophila melanogaster* neuromuscular junction and the mammalian visual cortex[84]. During development, negative feedback-based mechanisms globally alter synaptic strength to ensure that particular classes of neurons exhibit the appropriate number, size and function of synaptic connections. In the first few days or weeks after stroke, normal patterns of synaptic activity in peri-infarct[7,50,88–90] and even distant functionally related structures are interrupted[91]. This reduced activity is probably due to the loss of inputs from adjacent tissue that is affected by the infarct, oedema, reduced cerebral blood flow and metabolic depression[1]. Although it is not firmly implicated

in the case of stroke, homeostatic plasticity in the form of changes at existing synapses or new connections might reset the level of activity in these neurons. Evidence that this occurs after injury includes post-stroke hyperexcitability that develops over the first week to month of recovery — in rodents, this is reflected by expanded and less specific receptive fields and increased spontaneous activity[50,92]. Increased excitability in surviving neurons might also lead to the transient appearance of patterned low frequency spontaneous activity (of 0.1–1 Hz) that contributes to a permissive environment for axonal sprouting in rat focal ischaemia models[58]. Interestingly, this low frequency activity was observed only 1–3 days after stroke, suggesting that it has a critical period. Hyperexcitability correlates with a relative loss of inhibition and with changes in the intrinsic electrophysiological properties of neurons. These changes might be governed by alterations in receptor expression, phosphorylation, ion gradients[93] or other modulatory factors[94].

In addition to the regulation of synaptic activity, homeostatic mechanisms could trigger the formation of new synapses that would compensate for lost structural circuits. Thus, axonal sprouting[41,56,62,95] and increases in dendritic spine production after stroke[7,8] can be thought of as homeostatic processes that help to return post-stroke synaptic activity to target levels. The molecular determinants of homeostatic synaptic plasticity are only partly known. The pro-inflammatory cytokine tumour necrosis factor-α[96,97] and BDNF[98] are crucially involved in the upregulation of the insertion of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)-type glutamate receptors, which leads to enhanced synaptic efficacy. Conceivably, post-stroke inflammation might be associated with glial cytokine release, which leads to the upregulation of synaptic transmission in the peri-infarct zone, making it possible that the management of inflammation might actually reduce post-stroke plasticity.

The prevalence of homeostatic mechanisms across multiple animal models strengthens the prediction that they can affect human stroke recovery. Although somewhat counterintuitive, if one considers the well-described benefits of activity-inducing rehabilitation, there could be certain scenarios in which low levels of activity facilitate early stages of recovery. Clinically, there have been reports that very early physical therapy, especially if too intensive, might actually be detrimental to stroke recovery[99]. The intense early use of circuits that are promoted by physical therapy could block the advantage that is afforded by homeostatic mechanisms. However, homeostatic mechanisms might also be engaged as an obligate response to the post-stroke loss of circuitry. Even in the presence of activity stimulated by rehabilitative therapy, the peri-infarct tissue would perhaps have considerably lower overall activity, and activity stimulated by early therapy would not be detrimental. Nonetheless, the existence of mechanisms through which the presence or absence of activity can promote plasticity suggests the need for the careful examination of time windows and stroke presentation (for example, size, location and other features) when initiating activity-based therapies.
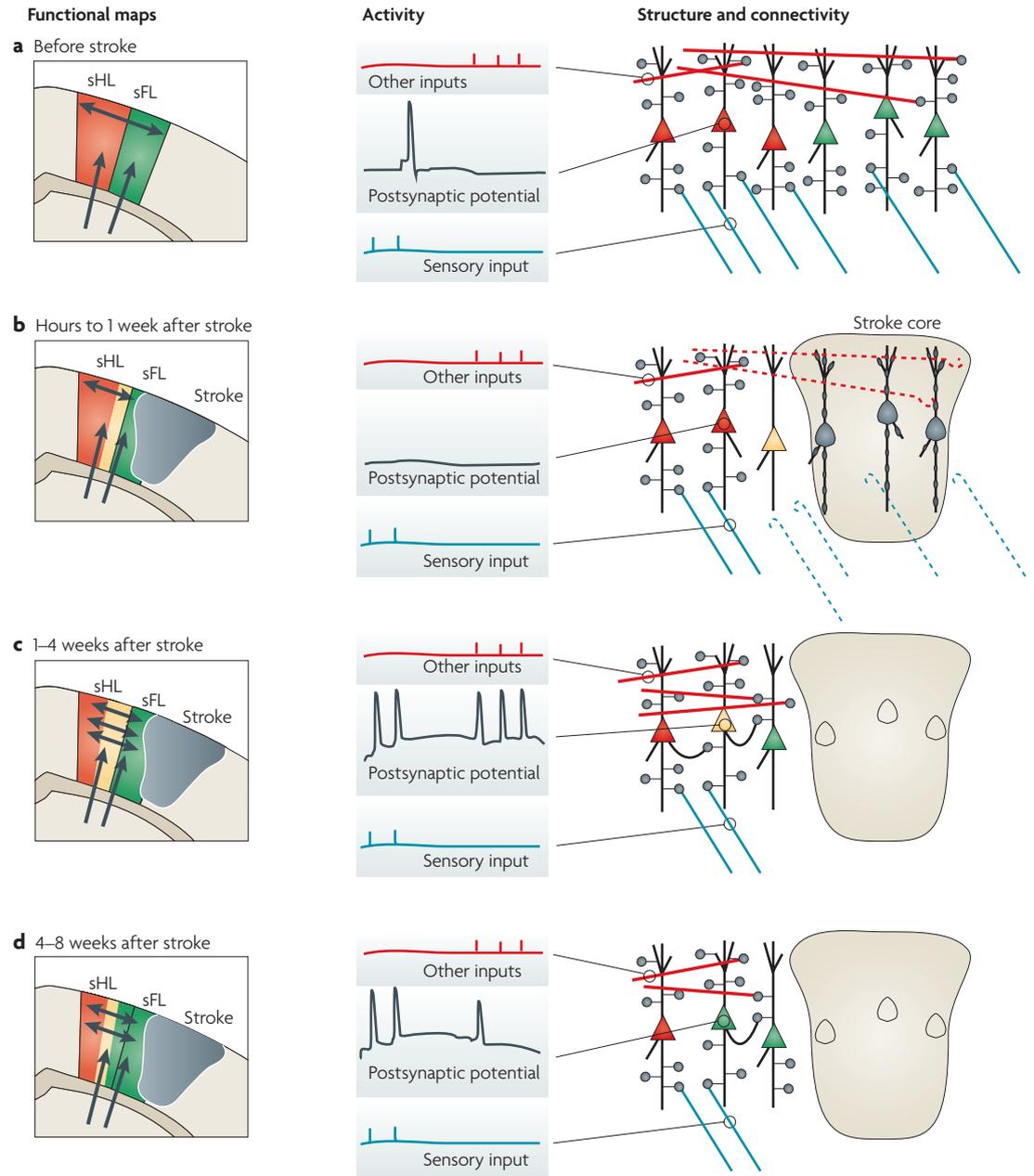
Functional maps

a Before stroke

Activity

Structure and connectivity

b Hours to 1 week after stroke

c 1–4 weeks after stroke

d 4–8 weeks after stroke

Figure 3 | **Time course and events associated with stroke recovery in the rodent peri-infarct zone.** The left column shows functional maps of the forelimb (sFL) and hindlimb (sHL) somatosensory cortex, with thalamic (arrows) and intracortical (double-headed arrows) projections. The middle column represents circuit activity that is stimulated by sensory or other inputs. The right column is a close-up of the functional border between the sHL (red) and sFL (green) areas. Blue lines represent thalamic input and red lines represent intracortical connections. **a** | Normal circuit structure in the mouse sFL. Sensory and other inputs generate infrequent action potentials in somatosensory neurons. **b** | During the first hours to days after stroke, neurons in the ischaemic core die (grey), whereas those near the border of this region might survive but lose dendritic spines (yellow)[8,162]. The yellow neurons and regions in the left column show areas of reduced sensory specificity, which are responsive to both FL and HL inputs[40]. Normal patterns of activity are disrupted and activity in surviving neurons is reduced[7,90]. **c** | Over 1–4 weeks after stroke, growth-promoting processes are elevated, these may be part of homeostatic processes that restore connectivity. New horizontal cortical axonal projections (double-headed arrows in the left column and red lines in the right column) form and peri-infarct dendritic spine turnover and synaptogenesis are increased[7,95,163]. Neurons become increasingly more excitable[118] and lack native sensory specificity[50,164]. Hyperexcitability and prolonged responses to sensory stimulation[7] might facilitate activity at other inputs, leading to coincidental presynaptic and postsynaptic activity and Hebbian synaptic strengthening. **d** | Up to 4–8 weeks after stroke, refinement of synaptic connections occurs, with greater specificity in sensory responses[50]. At this point, some sHL neurons have rewired to process information that was previously mediated by the infarct-affected region — sHL neurons now are selective for sFL. This is shown in the figure by the colour change of a neuron from red to green. The time courses shown reflect an approximate sequence of events and might vary between studies.

Ischaemia
Inadequate blood supply. The ischaemic core is the area with <20% blood flow during stroke, in which most neurons and glia will die.

Box 4 | Brain locations predicted to mediate stroke recovery
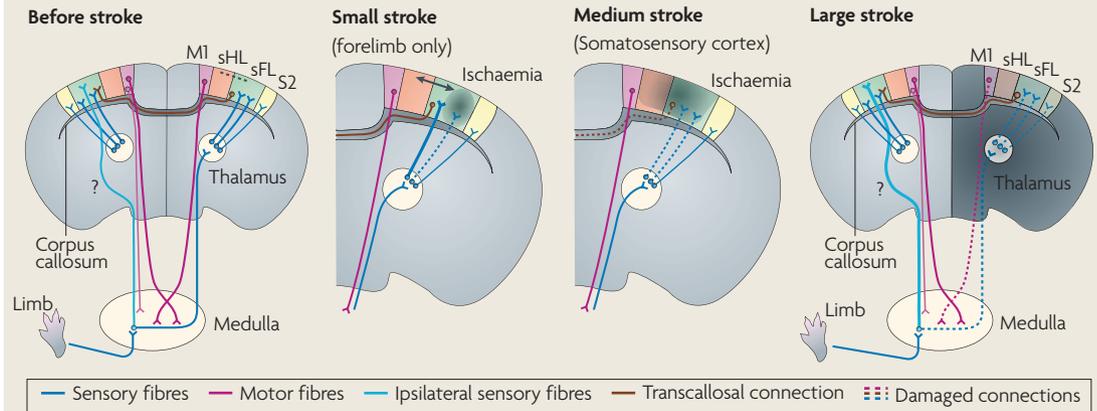
Here we provide a 'checklist' for the recovery of sensorimotor function after stroke. As an example we use a stroke that affects the rodent forelimb sensory cortex. The checklist is based on the concept that nearby tissues with similar sensorimotor function will contribute to the recovery process through a strengthening of diffuse synaptic connections or through the creation of new structural connections under the guidance of synaptic learning rules. The neural mechanisms by which these steps are followed are unclear; however, they are probably guided by established wiring principles[155–157] that result in an economy of connectivity and are consistent with the learning rules that we describe. Examples of normal contralateral and ipsilateral pathways are shown in the figure, as are cases of small, medium and large strokes in which the rules outlined below could be applied. The primary motor cortex (M1) and hindlimb (sHL), forelimb (sFL) and secondary somatosensory cortex (S2) are indicated.

Step 1
Are there any remaining thalamic connections to the primary or secondary somatosensory cortex in the affected hemisphere (as might be the case for small and medium stroke cases)? If so, proceed to step 2. If not, as might be observed after a large stroke, it might be necessary to find a route to the homotopic, contralesional sensory cortex, such as through an uncrossed ipsilateral sensory pathway (see step 5).

Step 2
Is there a way of sending motor signals out of the ipsilesional cortex? Specifically, are motor cortex and corticofugal fibres intact (as might be the case for small and medium strokes)? The survival of these tracts predicts continued recovery[35]. If these fibres remain intact, proceed to step 3. If they do not, as seen in large strokes, it becomes necessary to use the ipsilateral (or contralesional) motor pathway.

Step 3
Are there regions of primary sensory cortex nearby with related function that are spared from damage? For example, if a small stroke affects the forelimb sensory cortex, does any intact hindlimb sensory cortex remain? If so, these regions should undergo remapping and take over the function of the damaged area. If not, proceed to step 4.

Step 4
Can remapping take place in a related non-primary sensory area in the same hemisphere, such as S2 (in the case of a medium stroke, for example)? If not, proceed to step 5. It is also possible that motor or premotor areas may be the site of remapping.

Step 5
Enhance the relative contribution of existing ipsilateral sensory or motor circuits, such as in large strokes[29].

Hebbian plasticity. In keeping with the analogy of learning rules, once homeostatic mechanisms are engaged to restore both synaptic structural elements and function towards target levels, Hebbian or correlative mechanisms could reinforce the appropriate presynaptic and postsynaptic elements. Hebbian mechanisms are engaged when presynaptic and postsynaptic neurons are coincidently active and when neurotransmitter release occurs within only a few tens of milliseconds after a multi-input-stimulated postsynaptic action potential[83,100]. Following stroke, such coincident activity might show that a particular surviving circuit (or a new circuit formed by axonal sprouting) is functioning correctly with sufficient drive to produce postsynaptic action potentials that are paired with incoming presynaptic stimuli. As shown in FIG. 3,

prolonged sensory input-induced depolarizing responses in the peri-infarct region[7] might keep neurons near the threshold for longer and facilitate action potential-dependent activity at other functionally related inputs, leading to coincident activation. These coincidently active connections form a behaviourally relevant circuit and are selected for retention or strengthening. By contrast, synaptic connections that are activated out of phase might be incorrectly wired and are weakened. Slower persistently active circuits that are present in recovering animals[7] might increase the chance that peri-infarct connections are enhanced through coincident activity (FIG. 3).

Mounting evidence supports a fundamental role for Hebbian mechanisms in producing activity-dependent changes in synaptic strength in models of learning and

memory[101]. As with homeostatic mechanisms, direct evidence for Hebbian mechanisms after stroke is lacking; however, specific forms of use-dependent rehabilitative training (such as reach training for an impaired limb) can influence rewiring and functional outcome[6,17,102]. In patients, constraint-induced movement therapy (BOX 3) might help to channel coincident activity within circuits that subserve a stroke-affected limb[103]. Elegant studies in non-human primates and rodent models[104–106] have provided insights into the elements of this reorganizational process. For example, using intracortical microstimulation techniques in monkeys with small cortical infarcts in the primary motor cortex, it was shown that cortical representations of the hand region can be reconstituted in the peri-infarct tissue that normally subserves elbow and shoulder function. Importantly, these motor maps were reorganized only in monkeys that had reach training-based rehabilitation[17]. Although stroke-affected circuits might be inherently more plastic, their role in activity-dependent processes can be further enhanced by blocking activity in intact limbs[107,108]. Virtual reality training, in which, with the aid of computer software, patients imagine making movements, can even be beneficial[109]. Such training could enhance coincident activity, which strengthens specific synapses and potentially reduces efficacy at others. The presence of Hebbian mechanisms is further supported by the observation of facilitated long-term potentiation in brain slices from surviving peri-infarct tissues 7–10 days after stroke[110] and by the demonstration that patterned brain stimulation can improve stroke outcome in primates[111,112]. However, this approach might need further optimization for human patients[113]. How far this analogy extends and whether factors that influence Hebbian processes, such as long-term potentiation, will have an impact on stroke recovery is an area for further investigation.

A model of stroke recovery

We suggest a model in which homeostatic mechanisms during the initial stages of stroke recovery (the first 1–4 weeks) re-establish the activation of stroke-affected areas through both structural and functional changes to circuits. Assuming that the damaging effect of stroke spares some circuitry to route sensory signals to the brain and motor commands out of it, Hebbian-like, activity-dependent, synapse-based learning rules can strengthen and refine these circuits (FIG. 3). In regions with partial function, it is possible that the restoration of circuit activity could be facilitated over days to weeks through compensatory rewiring or remapping, as some of the original thalamic and intracortical connections are still present. These provide weak sensory or motor signals that are enhanced through plasticity[7] (BOX 4).

In this model, unmasked latent subthreshold inputs combined with new synaptogenesis lead to the remapping of function from damaged areas to peri-infarct surviving tissue[36,40]. Axonal sprouting[56,58,114], synaptogenesis[7,8] and cortical hyperexcitability (as a result of relatively reduced inhibition and increased glutamate transmission[92,115–118]) might facilitate subthreshold inputs after stroke. Findings from the examination of post-stroke sensory remapping

in mice with cellular resolution using two-photon Ca^{2+} imaging[50] were consistent with a transient loss of inhibition and the proliferation of functional connections, which possibly reflects the initial homeostatic plasticity phase. Individual layer 2 somatosensory neurons first increased their receptive field size to the point where, in some cases, previously limb-selective neurons responded to mechanical stimulation of all four limbs 1 month after stroke. Response selectivity increased 2 months after stroke, and single neurons responded predominantly to a single limb[50]. This is consistent with a general model in which an initial disinhibition and proliferation of new connections and the potentiation of surviving synapses is followed by Hebbian-type refinement of neural circuits (FIG. 3). Although we emphasize the role of adjacent cortical regions or even the homotypic, contralateral hemisphere (BOX 4; FIGS 1,3) in mediating recovery from cortical stroke damage, it is also apparent that there will be changes in subcortical sensorimotor regions, such as the spinal cord[62,119], and opportunistic transcallosal connections to the denervated striatum[58,120]. In the case of spinal cord injury, there is good evidence for the rerouting of both sensory and motor signals[121]. Subcortical reorganization after stroke might provide 'midline crossover points' that are crucial to re-establish normal routes of lateralized activation during recovery.

Plasticity rules and the patient

Strong rules for encouraging plasticity in animal models suggest avenues for translation to humans. Clearly, mechanisms in which activity can scale down synaptic strength (that is, mechanisms that can induce homeostatic plasticity) suggest that careful consideration of rehabilitation onset times, tailored training to the type and extent of stroke and the patient's history are required. However, it is possible that the stroke itself results in a loss of activity that is sufficient to engage homeostatic mechanisms without the need for therapeutic reduction in activity. Importantly, animal data suggest that homeostatic and Hebbian plasticity mechanisms can operate at the same time, leading to the scaling of total synaptic strength by homeostatic mechanisms and the re-distribution of synaptic strength to the appropriate coincidentally active synapses by Hebbian processes[122]. In animal models, BDNF has been shown to have a role in homeostatic plasticity[98], thereby supporting a link between plasticity rules and the patient, and common BDNF gene polymorphisms are associated with altered motor function[66,123,124]. Further strengthening the link, humans show BDNF polymorphism-dependent differences in a form of homeostatic plasticity that is evoked using transcranial magnetic stimulation[66]. With regard to Hebbian rule-based therapies, future work could use paradigms that are tailored to stimulate stroke-recovering circuits with temporal signatures that are designed to optimize the coincident activity of recovering circuits.

Future directions

One of the most important experimental challenges for the field will be to unambiguously link specific circuit changes to improved behaviour in recovering

animals. To investigate the effect of specific circuits, new genetically targeted tools, such as light-sensitive activators and inhibitors of neuronal function, could be applied[125–131]. After spinal cord injury, the brief activation of respiratory networks that express light-activated channelrhodopsin 2 is sufficient to restore the rhythmic activity associated with breathing[132]. Surprisingly, the breathing circuit maintains activity after only a brief priming with light stimulation. These results suggest that optical control of brain activity, like the less well targeted transcranial magnetic stimulation[113], could also be attempted as a means of stimulating stroke recovery.

It is possible that we might sometimes fail to correctly diagnose stroke and therefore we might have greatly underestimated its prevalence. Stroke is often referred to as the 'silent killer' because, unlike a heart attack, it strikes without warning. However, recent evidence has revealed an even more insidious form of stroke, termed covert stroke, which gradually erodes cognitive function in afflicted individuals owing to compromised small vessel perfusion. Covert stroke is distinguished by the fact that the obvious symptoms of stroke, such as paralysis, impaired speech production or comprehension and loss of vision, are not present. Recent studies have shown that the prevalence of covert stroke, which is often manifested subcortically, is several times higher in the general population than stroke and that it rises appreciably with age and in select patient populations, such as those with cardiovascular disease, depression, first ischaemic stroke and Alzheimer's disease[133–135]. Thus, generating animal models of vascular cognitive impairment and focusing on this more prevalent but less understood form of cerebrovascular disease would be prudent.

1. Hossmann, K. A. Pathophysiology and therapy of experimental stroke. *Cell. Mol. Neurobiol.* **26**, 1057–1083 (2006).
2. Murphy, T. H., Li, P., Betts, K. & Liu, R. 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**, 1756–1772 (2008).
3. Besancon, E., Guo, S., Lok, J., Tymianski, M. & Lo, E. H. Beyond NMDA and AMPA glutamate receptors: emerging mechanisms for ionic imbalance and cell death in stroke. *Trends Pharmacol. Sci.* **29**, 268–275 (2008).
4. Zhang, S. & Murphy, T. H. Imaging the impact of cortical microcirculation on synaptic structure and sensory-evoked hemodynamic responses *in vivo*. *PLoS Biol.* **5**, e119 (2007).
5. Doyle, K. P., Simon, R. P. & Stenzel-Poore, M. P. Mechanisms of ischemic brain damage. *Neuropharmacology* **55**, 310–318 (2008).
6. Biernaskie, J., Chernenko, G. & Corbett, D. Efficacy of rehabilitative experience declines with time after focal ischemic brain injury. *J. Neurosci.* **24**, 1245–1254 (2004).
   The first evidence for a 'critical period' for stroke recovery. Enriched rehabilitation in the first few weeks following stroke enhances the recovery of forelimb reaching and increases dendritic branching of cortical neurons. Delaying rehabilitation by 30 days is largely ineffective in restoring impaired upper limb function and does not alter cortical dendrites.
7. Brown, C. E., Aminoltejari, K., Erb, H., Winship, I. R. & Murphy, T. H. *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**, 1719–1734 (2009).
   The authors visualize the function of sensorimotor cortex circuitry after stroke with voltage-sensitive dyes. The results indicate slower kinetics in remapped sensory circuits that could possibly enhance the probability of Hebbian forms of synapse strengthening.
8. Brown, C. E., Li, P., Boyd, J. D., Delaney, K. R. & Murphy, T. H. Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. *J. Neurosci.* **27**, 4101–4109 (2007).
9. Carmichael, S. T. *et al.* Growth-associated gene expression after stroke: evidence for a growth-promoting region in peri-infarct cortex. *Exp. Neurol.* **193**, 291–311 (2005).
10. Cheatwood, J. L., Emerick, A. J. & Kartje, G. L. Neuronal plasticity and functional recovery after ischemic stroke. *Top. Stroke Rehabil.* **15**, 42–50 (2008).
11. Ploughman, M. *et al.* Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke* **40**, 1490–1495 (2009).
12. Cramer, S. C. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. *Ann. Neurol.* **63**, 272–287 (2008).
13. Whishaw, I. Q. Loss of the innate cortical engram for action patterns used in skilled reaching and the development of behavioral compensation following motor cortex lesions in the rat. *Neuropharmacology* **39**, 788–805 (2000).
    Demonstrates that functional recovery following stroke in most instances consists of compensatory movement strategies, instead of a return of the exact motor action patterns that existed prior to stroke.
14. Moon, S. K., Alaverdashvili, M., Cross, A. R. & Whishaw, I. Q. Both compensation and recovery of skilled reaching following small photothrombotic stroke to motor cortex in the rat. *Exp. Neurol.* **218**, 145–153 (2009).
15. Levin, M. F., Kleim, J. A. & Wolf, S. L. What do motor "recovery" and "compensation" mean in patients following stroke? *Neurorehabil. Neural Repair* **23**, 313–319 (2009).
16. Levin, M. F., Michaelsen, S. M., Cirstea, C. M. & Roby-Brami, A. Use of the trunk for reaching targets placed within and beyond the reach in adult hemiparesis. *Exp. Brain Res.* **143**, 171–180 (2002).
17. Nudo, R. J., Wise, B. M., SiFuentes, F. & Milliken, G. W. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science* **272**, 1791–1794 (1996).
    An elegant illustration of cortical motor function remapping in non-human primates following stroke. This form of neuroplasticity requires use-dependent experience as a result of rehabilitation.
18. Monfils, M. H., Plautz, E. J. & Kleim, J. A. In search of the motor engram: motor map plasticity as a mechanism for encoding motor experience. *Neuroscientist* **11**, 471–483 (2005).
19. Chen, J. *et al.* Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats. *Stroke* **32**, 1005–1011 (2001).
20. Lichtenwalner, R. J. & Parent, J. M. Adult neurogenesis and the ischemic forebrain. *J. Cereb. Blood Flow Metab.* **26**, 1–20 (2006).
21. Carmichael, S. T. Themes and strategies for studying the biology of stroke recovery in the poststroke epoch. *Stroke* **39**, 1380–1388 (2008).
22. Kolb, B. *et al.* Growth factor-stimulated generation of new cortical tissue and functional recovery after stroke damage to the motor cortex of rats. *J. Cereb. Blood Flow Metab.* **27**, 983–997 (2007).
23. Metz, G. A., Antonow-Schlorke, I. & Witte, O. W. Motor improvements after focal cortical ischemia in adult rats are mediated by compensatory mechanisms. *Behav. Brain Res.* **162**, 71–82 (2005).
24. Gharbawie, O. A. & Whishaw, I. Q. Parallel stages of learning and recovery of skilled reaching after motor cortex stroke: "oppositions" organize normal and compensatory movements. *Behav. Brain Res.* **175**, 249–262 (2006).
25. Buurke, J. H. *et al.* Recovery of gait after stroke: what changes? *Neurorehabil. Neural Repair* **22**, 676–683 (2008).
26. Kleim, J. A. & Jones, T. A. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J. Speech Lang. Hear. Res.* **51**, S225–S239 (2008).
27. Lashley, K. S. In search of the engram. *Symp. Soc. Exp. Biol.* **4**, 454–482 (1950).
28. Brus-Ramer, M., Carmel, J. B. & Martin, J. H. Motor cortex bilateral motor representation depends on subcortical and interhemispheric interactions. *J. Neurosci.* **29**, 6196–6206 (2009).
29. Gonzalez, C. L. *et al.* Evidence for bilateral control of skilled movements: ipsilateral skilled forelimb reaching deficits and functional recovery in rats follow motor cortex and lateral frontal cortex lesions. *Eur. J. Neurosci.* **20**, 3442–3452 (2004).
30. Cramer, S. C. *et al.* A functional MRI study of subjects recovered from hemiparetic stroke. *Stroke* **28**, 2518–2527 (1997).
31. Chollet, F. *et al.* The functional anatomy of motor recovery after stroke in humans: a study with positron emission tomography. *Ann. Neurol.* **29**, 63–71 (1991).
32. Biernaskie, J., Szymanska, A., Windle, V. & Corbett, D. Bi-hemispheric contribution to functional motor recovery of the affected forelimb following focal ischemic brain injury in rats. *Eur. J. Neurosci.* **21**, 989–999 (2005).
33. Ward, N. S., Brown, M. M., Thompson, A. J. & Frackowiak, R. S. Neural correlates of motor recovery after stroke: a longitudinal fMRI study. *Brain* **126**, 2476–2496 (2003).
34. Hsu, J. E. & Jones, T. A. Contralesional neural plasticity and functional changes in the less-affected forelimb after large and small cortical infarcts in rats. *Exp. Neurol.* **201**, 479–494 (2006).
35. Stinear, C. M. *et al.* Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* **130**, 170–180 (2007).
36. Jones, E. G. Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. *Annu. Rev. Neurosci.* **23**, 1–37 (2000).
37. Smits, E., Gordon, D. C., Witte, S., Rasmusson, D. D. & Zarzecki, P. Synaptic potentials evoked by convergent somatosensory and corticocortical inputs in raccoon somatosensory cortex: substrates for plasticity. *J. Neurophysiol.* **66**, 688–695 (1991).
38. Berger, T. *et al.* Combined voltage and calcium epifluorescence imaging *in vitro* and *in vivo* reveals subthreshold and suprathreshold dynamics of mouse barrel cortex. *J. Neurophysiol.* **97**, 3751–3762 (2007).
39. Ferezou, I. *et al.* Spatiotemporal dynamics of cortical sensorimotor integration in behaving mice. *Neuron* **56**, 907–923 (2007).
40. Sigler, A., Mohajerani, M. & Murphy, T. H. Imaging rapid re-distribution of sensory-evoked depolarization through existing cortical pathways after targeted stroke in mice. *Proc. Natl Acad. Sci. USA* **106**, 11759–11764 (2009).
41. Carmichael, S. T. Plasticity of cortical projections after stroke. *Neuroscientist* **9**, 64–75 (2003).

42. Jenkins, W. M. & Merzenich, M. M. Reorganization of neocortical representations after brain injury: a neurophysiological model of the bases of recovery from stroke. *Prog. Brain Res.* **71**, 249–266 (1987).

43. Lo, E. H. A new penumbra: transitioning from injury into repair after stroke. *Nature Med.* **14**, 497–500 (2008).

44. Zhang, S., Boyd, J., Delaney, K. & Murphy, T. H. Rapid reversible changes in dendritic spine structure *in vivo* gated by the degree of ischemia. *J. Neurosci.* **25**, 5333–5338 (2005).
First paper to demonstrate that ischaemia-induced loss of dendritic structure can reverse with reperfusion.

45. Li, P. & Murphy, T. H. Two-photon imaging during prolonged middle cerebral artery occlusion in mice reveals recovery of dendritic structure after reperfusion. *J. Neurosci.* **28**, 11970–11979 (2008).

46. Dirnagl, U., Iadecola, C. & Moskowitz, M. A. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci.* **22**, 391–397 (1999).

47. Merzenich, M. M. *et al.* Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience* **8**, 33–55 (1983).
Clear demonstration that functional remapping can occur in response to a lack of input in the adult cortex.

48. Merzenich, M. M. *et al.* Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience* **10**, 639–665 (1983).

49. Buonomano, D. V. & Merzenich, M. M. Cortical plasticity: from synapses to maps. *Annu. Rev. Neurosci.* **21**, 149–186 (1998).

50. Winship, I. R. & Murphy, T. H. *In vivo* calcium imaging reveals functional rewiring of single somatosensory neurons after stroke. *J. Neurosci.* **28**, 6592–6606 (2008).
***In vivo* imaging indicates that remapping of limb function after stroke is supported by individual neurons that begin to process information from multiple limbs.**

51. Cramer, S. C., Shah, R., Juranek, J., Crafton, K. R. & Le, V. Activity in the peri-infarct rim in relation to recovery from stroke. *Stroke* **37**, 111–115 (2006).

52. Frost, S. B., Barbay, S., Friel, K. M., Plautz, E. J. & Nudo, R. J. Reorganization of remote cortical regions after ischemic brain injury: a potential substrate for stroke recovery. *J. Neurophysiol.* **89**, 3205–3214 (2003).

53. Winship, I. R. & Murphy, T. H. Remapping the somatosensory cortex after stroke: insight from imaging the synapse to network. *Neuroscientist* 21 Jul 2009 (doi:10.1177/107385840 9333076).

54. Jablonka, J. A., Witte, O. W. & Kossut, M. Photothrombotic infarct impairs experience-dependent plasticity in neighboring cortex. *Neuroreport* **18**, 165–169 (2007).

55. Liauw, J. *et al.* Thrombospondins 1 and 2 are necessary for synaptic plasticity and functional recovery after stroke. *J. Cereb. Blood Flow Metab.* **28**, 1722–1732 (2008).

56. Stroemer, R. P., Kent, T. A. & Hulsebosch, C. E. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. *Stroke* **26**, 2135–2144 (1995).

57. Comelli, M. C. *et al.* Time course, localization and pharmacological modulation of immediate early inducible genes, brain-derived neurotrophic factor and trkB messenger RNAs in the rat brain following photochemical stroke. *Neuroscience* **55**, 473–490 (1993).

58. Carmichael, S. T. & Chesselet, M. F. Synchronous neuronal activity is a signal for axonal sprouting after cortical lesions in the adult. *J. Neurosci.* **22**, 6062–6070 (2002).

59. Dancause, N. *et al.* Extensive cortical rewiring after brain injury. *J. Neurosci.* **25**, 10167–10179 (2005).
Finds extensive rewiring of the primate sensory cortex after injury to motor cortex. The results indicate that ventral premotor cortex, although not the site of injury, undergoes reorganization after stroke damage to motor cortex and thereby receives new axonal inputs from somatosensory cortex.

60. Jones, T. A. & Schallert, T. Use-dependent growth of pyramidal neurons after neocortical damage. *J. Neurosci.* **14**, 2140–2152 (1994).
Provides one of the first demonstrations of the importance of behaviour for use-dependent modification of cortical neurons following a stroke-like cortical injury.

61. Cheatwood, J. L., Emerick, A. J., Schwab, M. E. & Kartje, G. L. Nogo-A expression after focal ischemic stroke in the adult rat. *Stroke* **39**, 2091–2098 (2008).

62. Lee, J. K., Kim, J. E., Sivula, M. & Strittmatter, S. M. Nogo receptor antagonism promotes stroke recovery by enhancing axonal plasticity. *J. Neurosci.* **24**, 6209–6217 (2004).

63. Papadopoulos, C. M. *et al.* Dendritic plasticity in the adult rat following middle cerebral artery occlusion and Nogo-a neutralization. *Cereb. Cortex* **16**, 529–536 (2006).

64. Hobohm, C. *et al.* Decomposition and long-lasting downregulation of extracellular matrix in perineuronal nets induced by focal cerebral ischemia in rats. *J. Neurosci. Res.* **80**, 539–548 (2005).

65. Schabitz, W. R. *et al.* Effect of brain-derived neurotrophic factor treatment and forced arm use on functional motor recovery after small cortical ischemia. *Stroke* **35**, 992–997 (2004).

66. Cheeran, B. *et al.* A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J. Physiol.* **586**, 5717–5725 (2008).

67. Au, E. *et al.* SPARC from olfactory ensheathing cells stimulates Schwann cells to promote neurite outgrowth and enhances spinal cord repair. *J. Neurosci.* **27**, 7208–7221 (2007).

68. Nudo, R. J. Mechanisms for recovery of motor function following cortical damage. *Curr. Opin. Neurobiol.* **16**, 638–644 (2006).

69. Carmichael, S. T. Cellular and molecular mechanisms of neural repair after stroke: making waves. *Ann. Neurol.* **59**, 735–742 (2006).

70. Linhoff, M. W. *et al.* An unbiased expression screen for synaptogenic proteins identifies the LRRTM protein family as synaptic organizers. *Neuron* **61**, 734–749 (2009).

71. Hubel, D. H. & Wiesel, T. N. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* **206**, 419–436 (1970).

72. Chakrabarty, S. & Martin, J. H. Postnatal development of the motor representation in primary motor cortex. *J. Neurophysiol.* **84**, 2582–2594 (2000).

73. Teitelbaum, P., Cheng, M. F. & Rozin, P. Development of feeding parallels its recovery after hypothalamic damage. *J. Comp. Physiol. Psychol.* **67**, 430–441 (1969).

74. Cramer, S. C. & Chopp, M. Recovery recapitulates ontogeny. *Trends Neurosci.* **23**, 265–271 (2000).

75. Hattiangady, B., Rao, M. S., Shetty, G. A. & Shetty, A. K. Brain-derived neurotrophic factor, phosphorylated cyclic AMP response element binding protein and neuropeptide Y decline as early as middle age in the dentate gyrus and CA1 and CA3 subfields of the hippocampus. *Exp. Neurol.* **195**, 353–371 (2005).

76. Horn, S. D. *et al.* Stroke rehabilitation patients, practice, and outcomes: is earlier and more aggressive therapy better? *Arch. Phys. Med. Rehabil.* **86**, S101–S114 (2005).

77. Salter, K. *et al.* Impact of early vs delayed admission to rehabilitation on functional outcomes in persons with stroke. *J. Rehabil. Med.* **38**, 113–117 (2006).

78. Teasell, R. W., Foley, N. C., Salter, K. L. & Jutai, J. W. A blueprint for transforming stroke rehabilitation care in Canada: the case for change. *Arch. Phys. Med. Rehabil.* **89**, 575–578 (2008).

79. Weinrich, M. *et al.* Timing, intensity, and duration of rehabilitation for hip fracture and stroke: report of a workshop at the National Center for Medical Rehabilitation Research. *Neurorehabil. Neural Repair* **18**, 12–28 (2004).

80. Pizzorusso, T. *et al.* Structural and functional recovery from early monocular deprivation in adult rats. *Proc. Natl Acad. Sci. USA* **103**, 8517–8522 (2006).

81. Silver, J. & Miller, J. H. Regeneration beyond the glial scar. *Nature Rev. Neurosci.* **5**, 146–156 (2004).

82. Massey, J. M. *et al.* Chondroitinase ABC digestion of the perineuronal net promotes functional collateral sprouting in the cuneate nucleus after cervical spinal cord injury. *J. Neurosci.* **26**, 4406–4414 (2006).

83. Song, S., Miller, K. D. & Abbott, L. F. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nature Neurosci.* **3**, 919–926 (2000).

84. Turrigiano, G. G. & Nelson, S. B. Homeostatic plasticity in the developing nervous system. *Nature Rev. Neurosci.* **5**, 97–107 (2004).

85. Hebb, D. O. *The Organization of Behavior: a Neuropsychological Theory* (Wiley, New York, 1949).

86. Butts, D. A., Kanold, P. O. & Shatz, C. J. A burst-based "Hebbian" learning rule at retinogeniculate synapses links retinal waves to activity-dependent refinement. *PLoS Biol.* **5**, e61 (2007).

87. Stellwagen, D. & Shatz, C. J. An instructive role for retinal waves in the development of retinogeniculate connectivity. *Neuron* **33**, 357–367 (2002).

88. Gao, T. M., Pulsinelli, W. A. & Xu, Z. C. Changes in membrane properties of CA1 pyramidal neurons after transient forebrain ischemia *in vivo*. *Neuroscience* **90**, 771–780 (1999).

89. Bolay, H. *et al.* Persistent defect in transmitter release and synapsin phosphorylation in cerebral cortex after transient moderate ischemic injury. *Stroke* **33**, 1369–1375 (2002).

90. Carmichael, S. T., Tatsukawa, K., Katsman, D., Tsuyuguchi, N. & Kornblum, H. I. Evolution of diaschisis in a focal stroke model. *Stroke* **35**, 758–763 (2004).

91. Butefisch, C. M., Netz, J., Wessling, M., Seitz, R. J. & Homberg, V. Remote changes in cortical excitability after stroke. *Brain* **126**, 470–481 (2003).

92. Schiene, K. *et al.* Neuronal hyperexcitability and reduction of GABA$_A$-receptor expression in the surround of cerebral photothrombosis. *J. Cereb. Blood Flow Metab.* **16**, 906–914 (1996).

93. Rivera, C. *et al.* The K$^+$/Cl$^-$ co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature* **397**, 251–255 (1999).

94. Xu, X., Ye, L. & Ruan, Q. Environmental enrichment induces synaptic structural modification after transient focal cerebral ischemia in rats. *Exp. Biol. Med. (Maywood)* **234**, 296–305 (2009).

95. Carmichael, S. T., Wei, L., Rovainen, C. M. & Woolsey, T. A. New patterns of intracortical projections after focal cortical stroke. *Neurobiol. Dis.* **8**, 910–922 (2001).

96. Stellwagen, D., Beattie, E. C., Seo, J. Y. & Malenka, R. C. Differential regulation of AMPA receptor and GABA receptor trafficking by tumor necrosis factor-α. *J. Neurosci.* **25**, 3219–3228 (2005).

97. Stellwagen, D. & Malenka, R. C. Synaptic scaling mediated by glial TNF-α. *Nature* **440**, 1054–1059 (2006).

98. Turrigiano, G. G. The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* **135**, 422–435 (2008).

99. Dromerick, A. W. *et al.* Very early constraint-induced movement during stroke rehabilitation (VECTORS): a single-center RCT. *Neurology* **73**, 195–201 (2009).

100. Song, S. & Abbott, L. F. Cortical development and remapping through spike timing-dependent plasticity. *Neuron* **32**, 339–350 (2001).

101. Whitlock, J. R., Heynen, A. J., Shuler, M. G. & Bear, M. F. Learning induces long-term potentiation in the hippocampus. *Science* **313**, 1093–1097 (2006).

102. Biernaskie, J. & Corbett, D. Enriched rehabilitative training promotes improved forelimb motor function and enhanced dendritic growth after focal ischemic injury. *J. Neurosci.* **21**, 5272–5280 (2001).
Shows that upper limb deficits that show little spontaneous recovery respond well to a form of enriched rehabilitation consisting of a combination of complex housing plus daily reach training.

103. Gauthier, L. V. *et al.* Remodeling the brain: plastic structural brain changes produced by different motor therapies after stroke. *Stroke* **39**, 1520–1525 (2008).

104. Castro-Alamancos, M. A. & Borrel, J. 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**, 793–805 (1995).

105. Kleim, J. A. *et al.* Motor cortex stimulation enhances motor recovery and reduces peri-infarct dysfunction following ischemic insult. *Neurol. Res.* **25**, 789–793 (2003).

106. Conner, J. M., Chiba, A. A. & Tuszynski, M. H. The basal forebrain cholinergic system is essential for cortical plasticity and functional recovery following brain injury. *Neuron* **46**, 173–179 (2005).

107. Sawaki, L. *et al.* Constraint-induced movement therapy results in increased motor map area in subjects 3 to 9 months after stroke. *Neurorehabil. Neural Repair* **22**, 505–513 (2008).

108. Ploughman, M. & Corbett, D. Can forced-use therapy be clinically applied after stroke? An exploratory randomized controlled trial. *Arch. Phys. Med. Rehabil.* **85**, 1417–1423 (2004).

109. Page, S. J., Szaflarski, J. P., Eliassen, J. C., Pan, H. & Cramer, S. C. Cortical plasticity following motor skill learning during mental practice in stroke. *Neurorehabil. Neural Repair* **23**, 382–388 (2009).

110. Hagemann, G., Redecker, C., Neumann-Haefelin, T., Freund, H. J. & Witte, O. W. Increased long-term potentiation in the surround of experimentally induced focal cortical infarction. *Ann. Neurol.* **44**, 255–258 (1998).

111. Plautz, E. J. *et al.* Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol. Res.* **25**, 801–810 (2003).

112. Harvey, R. L. & Nudo, R. J. Cortical brain stimulation: a potential therapeutic agent for upper limb motor recovery following stroke. *Top. Stroke Rehabil.* **14**, 54–67 (2007).

113. Plow, E. B., Carey, J. R., Nudo, R. J. & Pascual-Leone, A. Invasive cortical stimulation to promote recovery of function after stroke: a critical appraisal. *Stroke* **40**, 1926–1931 (2009).

114. Ng, S. C., de la Monte, S. M., Conboy, G. L., Karns, L. R. & Fishman, M. C. Cloning of human GAP-43: growth association and ischemic resurgence. *Neuron* **1**, 133–139 (1988).

115. Buchkremer-Ratzmann, I., August, M., Hagemann, G. & Witte, O. W. Electrophysiological transcortical diaschisis after cortical photothrombosis in rat brain. *Stroke* **27**, 1105–1109 (1996).

116. Domann, R., Hagemann, G., Kraemer, M., Freund, H. J. & Witte, O. W. Electrophysiological changes in the surrounding brain tissue of photochemically induced cortical infarcts in the rat. *Neurosci. Lett.* **155**, 69–72 (1993).

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

118. Redecker, C., Wang, W., Fritschy, J. M. & Witte, O. W. 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**, 1463–1475 (2002).

119. Lapash Daniels, C. M., Ayers, K. L., Finley, A. M., Culver, J. P. & Goldberg, M. P. Axon sprouting in adult mouse spinal cord after motor cortex stroke. *Neurosci. Lett.* **450**, 191–195 (2009).

120. McNeill, T. H., Brown, S. A., Hogg, E., Cheng, H. W. & Meshul, C. K. Synapse replacement in the striatum of the adult rat following unilateral cortex ablation. *J. Comp. Neurol.* **467**, 32–43 (2003).

121. Fouad, K. & Tse, A. Adaptive changes in the injured spinal cord and their role in promoting functional recovery. *Neurol. Res.* **30**, 17–27 (2008).

122. Turrigiano, G. G. & Nelson, S. B. Hebb and homeostasis in neuronal plasticity. *Curr. Opin. Neurobiol.* **10**, 358–364 (2000).

123. McHughen, S. A. *et al.* BDNF Val66Met polymorphism influences motor system function in the human brain. *Cereb. Cortex* 10 Sep 2009 (doi:10.1093/cercor/bhp189).

124. Kleim, J. A. *et al.* BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. *Nature Neurosci.* **9**, 735–737 (2006).

125. Airan, R. D., Thompson, K. R., Fenno, L. E., Bernstein, H. & Deisseroth, K. Temporally precise *in vivo* control of intracellular signalling. *Nature* **458**, 1025–1029 (2009).

126. Arenkiel, B. R. *et al. In vivo* light-induced activation of neural circuitry in transgenic mice expressing channelrhodopsin-2. *Neuron* **54**, 205–218 (2007).

127. Boyden, E. S., Zhang, F., Bamberg, E., Nagel, G. & Deisseroth, K. Millisecond-timescale, genetically targeted optical control of neural activity. *Nature Neurosci.* **8**, 1263–1268 (2005).

128. Gradinaru, V., Mogri, M., Thompson, K. R., Henderson, J. M. & Deisseroth, K. Optical deconstruction of parkinsonian neural circuitry. *Science* **324**, 354–359 (2009).

129. Gradinaru, V., Thompson, K. R. & Deisseroth, K. eNpHR: a *Natronomonas* halorhodopsin enhanced for optogenetic applications. *Brain Cell Biol.* **36**, 129–139 (2008).

130. Huber, D. *et al.* Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice. *Nature* **451**, 61–64 (2008).

131. Ayling, O. G., Harrison, T. C., Boyd, J. D., Goroshkov, A. & Murphy, T. H. Automated light-based mapping of motor cortex by photoactivation of channelrhodopsin-2 transgenic mice. *Nature Methods* **6**, 219–224 (2009).

132. Alilain, W. J. *et al.* Light-induced rescue of breathing after spinal cord injury. *J. Neurosci.* **28**, 11862–11870 (2008).

133. Vermeer, S. E., Longstreth, W. T. Jr & Koudstaal, P. J. Silent brain infarcts: a systematic review. *Lancet Neurol.* **6**, 611–619 (2007).

134. Longstreth, W. T. Jr *et al.* Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study. *Arch. Neurol.* **55**, 1217–1225 (1998).

135. Vermeer, S. E. *et al.* Silent brain infarcts and the risk of dementia and cognitive decline. *N. Engl. J. Med.* **348**, 1215–1222 (2003).

136. Longa, E. Z., Weinstein, P. R., Carlson, S. & Cummins, R. Reversible middle cerebral artery occlusion without craniectomy in rats. *Stroke* **20**, 84–91 (1989).

137. Carmichael, S. T. Rodent models of focal stroke: size, mechanism, and purpose. *NeuroRx* **2**, 396–409 (2005).
A thoughtful discussion of the advantages and disadvantages of commonly used animal stroke models as they relate to human stroke.

138. Zhang, Z. *et al.* A new rat model of thrombotic focal cerebral ischemia. *J. Cereb. Blood Flow Metab.* **17**, 123–135 (1997).

139. Hainsworth, A. H. & Markus, H. S. Do *in vivo* experimental models reflect human cerebral small vessel disease? A systematic review. *J. Cereb. Blood Flow Metab.* **28**, 1877–1891 (2008).

140. Sharkey, J., Ritchie, I. M. & Kelly, P. A. Perivascular microapplication of endothelin-1: a new model of focal cerebral ischaemia in the rat. *J. Cereb. Blood Flow Metab.* **13**, 865–871 (1993).

141. Windle, V. *et al.* An analysis of four different methods of producing focal cerebral ischemia with endothelin-1 in the rat. *Exp. Neurol.* **201**, 324–334 (2006).

142. Watson, B. D., Dietrich, W. D., Busto, R., Wachtel, M. S. & Ginsberg, M. D. Induction of reproducible brain infarction by photochemically initiated thrombosis. *Ann. Neurol.* **17**, 497–504 (1985).

143. Schaffer, C. B. *et al.* Two-photon imaging of cortical surface microvessels reveals a robust redistribution in blood flow after vascular occlusion. *PLoS Biol.* **4**, e22 (2006).

144. Zhang, L., Chen, J., Li, Y., Zhang, Z. G. & Chopp, M. Quantitative measurement of motor and somatosensory impairments after mild (30 min) and severe (2 h) transient middle cerebral artery occlusion in rats. *J. Neurol. Sci.* **174**, 141–146 (2000).

145. Montoya, C. P., Campbell-Hope, L. J., Pemberton, K. D. & Dunnett, S. B. The "staircase test": a measure of independent forelimb reaching and grasping abilities in rats. *J. Neurosci. Methods* **36**, 219–228 (1991).

146. Whishaw, I. Q., Pellis, S. M., Gorny, B., Kolb, B. & Tetzlaff, W. Proximal and distal impairments in rat forelimb use in reaching follow unilateral pyramidal tract lesions. *Behav. Brain Res.* **56**, 59–76 (1993).

147. Metz, G. A. & Whishaw, I. Q. Cortical and subcortical lesions impair skilled walking in the ladder rung walking test: a new task to evaluate fore- and hindlimb stepping, placing, and co-ordination. *J. Neurosci. Methods* **115**, 169–179 (2002).

148. Bliss, T., Guzman, R., Daadi, M. & Steinberg, G. K. Cell transplantation therapy for stroke. *Stroke* **38**, 817–826 (2007).

149. The STEPs Participants. Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS): bridging basic and clinical science for cellular and neurogenic factor therapy in treating stroke. *Stroke* **40**, 510–515 (2009).

150. Taub, E. *et al.* Technique to improve chronic motor deficit after stroke. *Arch. Phys. Med. Rehabil.* **74**, 347–354 (1993).
The original description of constraint-induced movement therapy, which has been shown to be perhaps the most effective method for producing functional gains months or years after the initial stroke injury.

151. Taub, E., Uswatte, G., Mark, V. W. & Morris, D. M. The learned nonuse phenomenon: implications for rehabilitation. *Eura Medicophys.* **42**, 241–256 (2006).

152. Feeney, D. M., Gonzalez, A. & Law, W. A. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. *Science* **217**, 855–857 (1982).

153. Gladstone, D. J. & Black, S. E. Enhancing recovery after stroke with noradrenergic pharmacotherapy: a new frontier? *Can. J. Neurol. Sci.* **27**, 97–105 (2000).

154. Lim, D. H., Alaverdashvili, M. & Whishaw, I. Q. Nicotine does not improve recovery from learned nonuse nor enhance constraint-induced therapy after motor cortex stroke in the rat. *Behav. Brain Res.* **198**, 411–419 (2009).

155. Ramón y Cajal, S. *Textura Del Sistema Nervioso Del Hombre Y De Los Vertebrados: Estudios Sobre El Plan Estructural Y Composición Histológica De Los Centros Nerviosos Adicionados De Consideraciones Fisiológicas Fundadas En Los Nuevos Descubrimentos* (Moya, Madrid, 1899) (in Spanish).

156. Ramón y Cajal, S., Pasik, P. & Pasik, T. *Texture Of The Nervous System Of Man And The Vertebrates* (Springer, New York, 1999).

157. Chen, B. L., Hall, D. H. & Chklovskii, D. B. Wiring optimization can relate neuronal structure and function. *Proc. Natl Acad. Sci. USA* **103**, 4723–4728 (2006).

158. Dijkhuizen, R. M. *et al.* Functional magnetic resonance imaging of reorganization in rat brain after stroke. *Proc. Natl Acad. Sci. USA* **98**, 12766–12771 (2001).

159. Wade, D. T., Langton-Hewer, R., Wood, V. A., Skilbeck, C. E. & Ismail, H. M. The hemiplegic arm after stroke: measurement and recovery. *J. Neurol. Neurosurg. Psychiatry* **46**, 521–524 (1983).

160. Grabowski, M., Brundin, P. & Johansson, B. B. Paw-reaching, sensorimotor, and rotational behavior after brain infarction in rats. *Stroke* **24**, 889–895 (1993).

161. Maulden, S. A., Gassaway, J., Horn, S. D., Smout, R. J. & DeJong, G. Timing of initiation of rehabilitation after stroke. *Arch. Phys. Med. Rehabil.* **86**, S34–S40 (2005).

162. Brown, C. E., Wong, C. & Murphy, T. H. Rapid morphologic plasticity of peri-infarct dendritic spines after focal ischemic stroke. *Stroke* **39**, 1286–1291 (2008).

163. Carmichael, S. T. Gene expression changes after focal stroke, traumatic brain and spinal cord injuries. *Curr. Opin. Neurol.* **16**, 699–704 (2003).

164. Reinecke, S., Dinse, H. R., Reinke, H. & Witte, O. W. Induction of bilateral plasticity in sensory cortical maps by small unilateral cortical infarcts in rats. *Eur. J. Neurosci.* **17**, 623–627 (2003).

165. Takatsuru, Y. *et al.* Neuronal circuit remodeling in the contralateral cortical hemisphere during functional recovery from cerebral infarction. *J. Neurosci.* **29**, 10081–10086 (2009).

166. Li, S. & Carmichael, S. T. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. *Neurobiol. Dis.* **23**, 362–373 (2006).
Provides evidence that axonal growth programmes are initiated in the aged rodent brain after stroke. This study also provides a comprehensive list of changes in gene expression and suggests parallels to development.

DATABASES
Entrez Gene:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
CAP23
UniProtKB: http://www.uniprot.org
BDNF | EPHB1 | ephrin A5 | GAP43 | MARCKS | neuropilin 1 | NOGO | semaphorin 3A | SPARC

FURTHER INFORMATION
Timothy H. Murphy's homepage:
http://www.neuroscience.ubc.ca/faculty/murphy.html
Dale Corbett's homepage:
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