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Motor compensation and its effects on neural reorganization after stroke

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Abstract

Stroke instigates a dynamic process of repair and remodelling of remaining neural circuits, and this process is shaped by behavioural experiences. The onset of motor disability simultaneously creates a powerful incentive to develop new, compensatory ways of performing daily activities. Compensatory movement strategies that are developed in response to motor impairments can be a dominant force in shaping post-stroke neural remodelling responses and can have mixed effects on functional outcome. The possibility of selectively harnessing the effects of compensatory behaviour on neural reorganization is still an insufficiently explored route for optimizing functional outcome after stroke.

Behavioural compensation refers to alternative behavioural strategies that circumvent impairments to enable the performance of tasks and the attainment of goals. The development of compensatory strategies after CNS damage is observed across diverse impairment modalities. For example, patients who have undergone callosotomy (and who are referred to as ‘split-brain’ individuals) develop peripheral self-cuing strategies to compensate for impaired interhemispheric communication¹. People with partial visual field loss use compensatory head and eye movements to help to fill in the field². Those with agrammatic aphasia compensate for impaired syntax comprehension by relying on semantics to understand speech³.

The compensatory strategies for stroke-induced motor disability are a prevalent category owing to the overwhelming prevalence of stroke. As of 2013, there were more than 25 million stroke survivors worldwide⁴, and this population is predicted to reach 70 million by 2030 (REF. 5). Up to 85% of stroke survivors have hemiparesis that affects the upper extremity (hand and arm) of one side⁶. Humans use both hands together most of the time⁷, and the loss of the function of either hand requires major adjustments to our interactions with the physical world. A common response to this loss after stroke is to learn compensatory ways of relying on the better-functioning, non-paretic hand^{8,9}. There are also compensatory changes in the coordination of movements of both hands and of the paretic forearm with the trunk, as explained below.

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Competing interests statement

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Compensation is often mistaken for recovery (BOX 1). One goal of this Review is to highlight the importance of distinguishing between the two in research on the neural mechanisms of recovery. Motor recovery is defined as the return of more-normal movement, or reductions in movement impairment. Some forms of compensation are obvious, but others are subtle enough to go undetected in the absence of sensitive behavioural measures, making them easily confused with recovery¹⁰. If not for the clever assays developed by Gazzaniga and colleagues¹, the use of self-cuing strategies in patients who have undergone callosotomy would be easy to miss and could be interpreted as support for the idea that these patients recovered interhemispheric communication without a key anatomical pathway for it. The failure to recognize compensatory strategies has a strong potential to confuse our understanding of the neural mechanisms of functional improvement after brain injury and to hamper the usefulness of basic neuroscience research for guiding treatment.

Another reason to attend to compensation is that it is both a mechanism for improved function and a contributor to persisting impairment after CNS injury^{8,10,11}. There is currently much interest in the potential to optimize functional outcome after CNS damage by capitalizing on early endogenous mechanisms of neural repair and remodelling after stroke, which are sensitive to behavioural manipulation and could facilitate the efficacy of motor rehabilitation^{12–15}. Behavioural compensation is often a major contributor to the functional improvements that result from motor rehabilitative training^{16,17}. Compensatory behaviours are also self-taught. As they are developed early and are well practised⁷, these selftaught behaviours may normally be a dominant force in shaping post-stroke brain reorganization; however, they may do so in suboptimal, or even maladaptive, ways.

From the perspective of a researcher of rodent models of chronic stroke, this Review first attempts to jointly summarize findings from human and animal studies on the nature of motor compensation after strokes that impair upper-limb function. I describe findings from animal models on the influence of motor compensation on neural reorganization after stroke and its maladaptive consequences, and briefly consider the potential impact of motor compensation on the role of the contralesional hemisphere in functional outcome.

Compensatory movement strategies

Stroke damage and its effects on movement.

The high prevalence of motor impairments after stroke may be due to the propensity for strokes to damage motor regions of cortex, the subcortical projection pathways of these regions or both^{18,19}, thus disrupting the cortical control of movement (FIG. 1). Post-stroke motor impairments are characterized by weakness, diminished muscle activation, abnormal muscle co-activation and other abnormalities that diminish movement capacity and disrupt the spatiotemporal coordination of movements^{20–23}. There is often abnormal coupling of shoulder and elbow movements (muscle synergies) — for example, the elbow may bend as the arm is lifted^{20,21,24}. Reduced wrist stability, diminished finger and grasp control, and impaired grasp release all impair hand dexterity^{25–27}. Movements are slower and more variable^{27,28}, reach trajectories are less direct²⁹, and more-extraneous movements occur³⁰ in stroke survivors than in healthy controls. Although the movements of both the left and the right hands are typically impaired after unilateral stroke, the non-paretic side is less severely

so^{31–34}. Spasticity due to hyperexcitability of the stretch reflex can develop after stroke³⁵, and its severity is correlated with the severity of motor impairments³⁶. Motor impairments co-occur to varying degrees with impaired somatosensation^{37,38}, which is associated with damage to ascending somatosensory pathways³⁹.

Movement adaptations after stroke.

There are normally many different ways (or degrees of freedom) in which individual joint movements can be combined to perform a task, and this diversity allows for adaptation to changing environmental conditions and movement constraints. Motor impairments after stroke can demand adaptation for a greatly diminished repertoire of movement combinations^{20,40,41}. Some of the compensatory movements that have been observed in stroke survivors or in animal models of stroke are described in TABLE 1. To perform reaching or pointing tasks with the paretic upper limb in laboratory settings, stroke survivors compensate for limited arm extension and stability using movements of the trunk and scapula^{42–45} (FIG. 2). The aim and orientation of the hand tend to be controlled more proximally by trunk and scapular movements, with elbow and hand positions fixed^{46,47}, a strategy that may reduce the complexity of movement control and increase stability^{42,48,49}. To grasp an object, stroke survivors use an excess of forward movements when reaching towards it⁵⁰ and use the resistance of the object to wind their fingers around it²⁵, presumably to compensate for impairments in opening the fingers to grasp. Those with milder impairments reach for differently sized objects using greater-than-normal adjustment at proximal, in place of distal, finger joints and make these adjustments later in the reach than normal, possibly reflecting a greater reliance on visual feedback to compensate for impaired feedforward control⁵¹. Those with milder impairments open the hand excessively to grasp objects and hold them with excessive grip force^{31,52,53}, which may help to ensure a successful grasp and hold in the presence of diminished hand control⁵³.

In the laboratory, stroke survivors who are not told which hand to use will typically perform unimanual tasks with the non-paretic hand^{54,55}. Outside of the laboratory, increased reliance on the non-paretic hand is a dominant strategy⁹. Based on data recorded with movement monitors worn on the wrists, healthy controls perform most daily activities using both hands^{7,56}. After strokes affecting the dominant body side, bilateral hand use is diminished, and sole use of the formerly non-dominant hand is increased in these patients relative to healthy controls^{7,56}. After strokes affecting the non-dominant side, use of only the dominant hand predominates^{7,56,57}. The non-paretic side is also used to help to move the paretic leg during walking, via amplified swinging movements with the non-paretic arm and leg⁴⁸.

Compensatory movement strategies are likely to be mediated by CNS regions that are less severely affected by the injury. Relying on the better-functioning hand puts the relatively intact circuitry of the contralesional hemisphere mostly in charge of task completion. In healthy individuals, there is more bilateral control of trunk, relative to limb, movements^{58,59}, and trunk movements are also used to reach for objects outside of arm's reach⁶⁰; thus, trunk movements may offer a ready solution for impaired arm extension after stroke.

Movement adaptations in animal models.

There are remarkable homologies in the movement patterns used by rodents and humans to perform reach-to-grasp tasks^{61,62}. There is also resemblance in the impairments and compensatory movement patterns that result from unilateral motor system damage^{63–66} (FIG. 2d–f). Slower, more-variable and more-extraneous movements are observed in the paretic forelimb of rodents after motor system damage than in intact animals^{65,67,68}. To reach for food rewards with the paretic forelimb, rodents use compensatory rotational movements of the trunk to extend and control paw position, and use compensatory trunk and head movements to bring the mouth to the paw^{16,63,69}. If not constrained, the non-paretic limb is often used to assist paretic limb movements — for example, to support the paretic forelimb during its extension (FIG. 2f) or to help to open its digits so that food can be released into the mouth^{13,16}. In addition, rats rely more on the non-paretic forelimb for activities such as food handling^{70,71} and postural support during exploration⁷².

Impairments in fine manual dexterity have been characterized in monkeys after focal motor system damage^{73,74} — for example, in tasks in which food rewards are most efficiently retrieved using a precision grip. After ischaemic lesions of the digit region of the primary motor cortex (M1)^{75,76} or of the posterior limb of internal capsule⁷⁷, macaques compensate for impairments in precision grip by scooping food rewards with one or more digits towards the palm or proximal thumb. However, these movement strategies can change with task practice, as described below.

Learning to compensate

Compensation is likely to begin whenever a stroke survivor first attempts to perform an activity with the paretic body side in the normal way that they did before the stroke, at which point it becomes evident that the normal way no longer works. That is, compensation can be expected to begin with the resumption of movement very early after stroke, but the process of becoming adept in the new ways of moving involves motor skill learning, which is practice dependent⁷⁸. A right-hander can manage to eat and dress using only the left hand, but the speed and efficiency in doing so is likely to improve over time with practice. Even long after stroke, new compensatory movement patterns can be developed in response to motor training¹⁰.

Learned non-use.

The counterpart of the compensatory strategy of relying mostly on the non-paretic hand is disuse of the paretic upper limb. This disuse has been proposed to result from ‘learned non-use’, whereby repeated experience with the weakness and ineptitude of stroke-impaired functions encourages their disuse⁸. This idea was originally based on observations in macaque monkeys with peripheral sensory deafferentation of one arm, which the monkeys continued to disuse even after its capacity to move returned⁷⁹. Findings in rats suggest that paretic limb disuse develops with repeated experiences in attempting to use it. Most rats have a strong preference for performing unimanual skilled reaching tasks with one limb. If this limb becomes paretic owing to large motor cortical or mixed cortical–subcortical lesions, rats continue to attempt to retrieve food rewards with it at first⁸⁰. However, after

repeated failures, they start attempting to retrieve rewards with the other limb. With continued practice, most rats with substantial injuries completely switch ‘handedness’ for reaching^{80,81}. Even rats that are not allowed to switch limbs (FIG. 2) transiently reduce their attempts to retrieve food rewards with the paretic limb after initial attempts are unsuccessful⁸².

In people who have survived stroke, the reliance on the trunk and scapula to control the position of the paretic hand can also encourage the disuse of more-distal movements of the paretic upper limb. Stroke survivors with moderate impairments who practise a reaching task with the paretic upper limb while the trunk is restrained regain more-normal elbow movement during arm extension, whereas those who do so without trunk restraint increase their reliance on compensatory trunk movements instead⁸³.

Training-induced compensation.

The compensatory movement patterns that develop after stroke can be self-taught or encouraged by interventions. Stroke rehabilitation is focused on improving functional abilities, and this improvement can be achieved through either the development of new compensatory strategies or the recovery of more-normal function. The relative contribution of the two varies with impairment level, with compensation making a larger contribution in those with more severe impairment^{42,84}, and with different rehabilitation approaches — for example, depending on the extent of guided movement and the restriction of compensatory strategies^{83,85,86}. However, most motor rehabilitation approaches are focused on successful task completion, which is permissive of compensation. In fact, some interventions encourage reliance on the non-paretic hand to perform basic daily tasks, such as dressing^{87,88}.

Rehabilitation efficacy can depend on compensation even when use of the non-paretic arm is restricted. Constraint-induced movement therapy (CIMT) involves constraint of the non-paretic arm during most waking hours while the paretic side undergoes intense task-oriented practice. CIMT has mostly been studied in stroke survivors who have some residual capacity to move the wrist and fingers. In one such study⁸⁹, CIMT improved performance on the Action Research Arm Test (which does not discriminate between recovery and compensation) but led to no notable improvements in measures of movement quality and impairment recovery. Several studies have found that CIMT improves the speed, efficiency and smoothness of paretic arm movements^{90–92}, but one of these studies⁹² found that it does so without diminishing reliance on compensatory trunk movements; in fact, reliance on such movements was increased after CIMT. Together, these findings suggest that CIMT may promote the refinement of compensatory movement strategies that improve the functional capacity of the paretic arm.

Several studies in rodent models of stroke have found that a few weeks of daily training of the paretic forelimb in skilled reaching tasks can improve performance (as measured by the successful retrieval of food rewards), even when abnormalities in the paretic limb movements that are used to perform the task persist, suggesting that the improvements result from compensatory strategies^{68,69,93,94}. In rats with substantial motor cortical infarcts, the performance improvements were greatly diminished if the non-paretic forelimb was kept in a sling during daily training, indicating that assistive movements of this limb probably

contributed to the improvements¹⁶. After smaller motor cortical infarcts that result in less-severe impairments, extensive training of the paretic limb in skilled reaching tasks promoted the normalization of some movements, whereas abnormalities in others — including wrist movements — persisted^{16,95}.

Findings in macaques with small M1 lesions indicate that the relative contributions of compensation and recovery to motor performance improvements can depend on the amount of task practice⁹⁶. M1 lesions impaired the performance of a precision grip task, but with daily post-lesion training on the task, the monkeys initially improved their performance using an alternative grip pattern that involved holding the food between the index fingertip and the proximal thumb. Over the course of weeks of daily training, the opposition moved more distally on the thumb surface, and eventually the original precision grip pattern (fingertip to thumb tip) returned. By contrast, there was no return of the original precision grip pattern in monkeys that received no training over the same time span. Thus, practising compensatory strategies that sufficiently approximate the original movement pattern might encourage the recovery of the original movement pattern.

Compensation-driven neural plasticity

Compensation involves learning and can be expected to depend on learning-associated neural plasticity mechanisms, but it begins while the brain is also undergoing widespread repair, regrowth and remodelling of the connectivity patterns of surviving neurons after stroke. Learning-related neural changes can interact with these regenerative responses to stroke¹³.

Regenerative responses to stroke.

The degeneration of neurons and their processes during and after a stroke instigates widespread regenerative counter-reactions, the end result of which is a reorganization of the synaptic connectivity patterns of surviving neurons. Axonal degeneration is a trigger for remaining axons near denervated regions to sprout new collaterals and to form synapses with newly denervated neurons^{97–99}. This is accompanied by dendritic restructuring^{100–102} and highly coordinated changes in glia and vasculature^{13,103,104}, as reviewed elsewhere^{105,106}. This regenerative process proceeds in many different brain regions to variable degrees and follows various time courses, depending on the anatomical connectivity of the injured region¹⁰⁷. Tissue near the core region of damage, and all areas that previously had substantial direct afferent or efferent projections to or from the damaged area, can be expected to undergo regenerative responses, such that even focal stroke results in widespread and bihemispheric changes in synaptic connectivity patterns. These regenerative processes occur over long time spans (months or longer), but they are particularly dynamic early (days to weeks) after stroke^{105,108}. The resulting alterations in synaptic connectivity patterns presumably contribute to clinical observations of altered intrahemispheric and interhemispheric inhibitory and excitatory activity^{109–111}, and changes in functional activation, as detected by, for example, functional MRI^{112,113}.

Effects of experience on regenerative responses.

Neural, as well as glial and vascular, remodelling responses to stroke are very sensitive to behavioural manipulations¹³. For example, in rodent studies, axonal sprouting patterns^{99,114,115}, synaptogenesis¹¹⁶, dendritic growth responses¹¹⁷ and astrocytic reactions¹¹⁸ are affected by post-injury manipulation of forelimb use. This sensitivity to behavioural experience may be explained by the neural activity dependence of post-stroke regenerative responses. More-active neural pathways are more likely than less-active ones to sprout new axons that contribute to re-innervation, as supported by findings that electrical stimulation promotes, and neural activity blockade reduces, the sprouting of specific pathways^{119–121}. Dendritic, synaptic, astrocytic^{122,123} and vascular¹²⁴ remodelling responses all depend on neural activity. Thus, it seems reasonable to predict that any behavioural experiences that sufficiently alter activity in circuits undergoing remodelling will influence the resulting pattern of neural connectivity.

Effects of compensation with the non-paretic limb.

Compensation with the non-paretic upper limb has a strong potential to influence neural remodelling responses after stroke, given that it is practised often⁷ and begins to develop very early after stroke⁹, when regenerative responses are likely to be particularly dynamic. Findings in rodent models of post-stroke upper-extremity impairments support this possibility (FIG. 3). Unilateral lesions in the forelimb region of M1 in rats result in compensatory reliance on the non-paretic forelimb, as well as a robust amount of dendritic growth and synapse proliferation in the contralesional homotopic cortex^{72,125}. Neuronal growth responses in the contralesional M1 are initiated by the degeneration of transcallosal projections from the opposite M1, making the contralesional M1 a point of convergence for regenerative responses and for the influence of behavioural compensation with the non-paretic forelimb. A series of studies established that neuronal growth responses in the contralateral M1 do in fact result from this convergence, as reviewed elsewhere¹²⁶. For example, forcing the use of one forelimb, to mimic compensatory reliance on one limb alone, or transecting callosal fibres, to reproduce the degenerative signals alone, each results in only subtle dendritic changes in the motor cortex^{101,127}. By contrast, forced use of one forelimb after callosal transection results in a dendritic growth response in the M1 contralateral to this forelimb that resembles the response found contralateral to unilateral M1 lesions.

Regenerative reactions also influence behavioural change. As explained above, the neuronal growth response to increased reliance on one forelimb is amplified in the corresponding M1 shortly after the transection of its transcallosal afferents^{101,127}. The neuronal growth response in the contralesional M1 to skill training of the non-paretic limb is similarly amplified, and this, in turn, is reflected in an increase in the learning capacity for this limb. Despite the presence of subtle motor impairments in the non-paretic forelimb, animals with M1 injuries show an accelerated and augmented acquisition of skilled reaching tasks with this limb compared with sham-operated animals^{128,129}. Thus, regenerative reactions can facilitate the development of compensatory strategies involving the use of the non-paretic limb.

Effects of paretic limb compensation?

Unlike the non-paretic limb, movements of the paretic limb are not normally well practised during the early periods of neural remodelling. However, there has been much interest in initiating rehabilitative interventions earlier after stroke, to capitalize on the pro-growth environment of the early remodelling period^{13–15,108}. Training the paretic forelimb in skilled motor tasks can promote new dendrite and synapse formation in peri-infarct motor cortex in rats¹¹⁷ and can induce the reorganization of surviving movement representations of the paretic forelimb in residual motor cortex of rodents and monkeys^{116,130–133} (FIG. 3). In the chronic period (>3 months) after stroke in humans, CIMT increases the size of motor cortical output maps of the paretic hand in the injured hemisphere, as assessed using transcranial magnetic stimulation (TMS) mapping^{134,135}. These neural substrates of rehabilitative training-induced improvements may be facilitated in the early pro-neuronal growth environment^{12,99}. Consistent with this, animal and clinical findings indicate that earlier post-stroke onsets of motor rehabilitative training tend to be more effective in improving behavioural function on the paretic side^{136–138} and in promoting reorganization of peri-infarct motor cortex¹³⁹ than do later ones. However, whether earlier interventions promote greater recovery, or simply more-effective compensation, has not yet been determined. Given that compensation is often a major contributor to motor training-induced performance improvements after stroke, it is reasonable to suspect that the time sensitivity of its efficacy could reflect time sensitivity in learning effective ways of compensating, rather than, or in addition to, recovery.

At present, there is not a precise understanding of the distinction between the neural mechanisms of practice-dependent improvements in the performance of the paretic upper limb that are due to the recovery of more-normal movement versus those that are due to the development of compensatory strategies. In squirrel monkeys with focal M1 infarcts, improvements in the performance of the paretic hand in a rehabilitative training task were due to the establishment of new movement patterns in some monkeys and to the recovery of the original movement patterns in others⁷³. There was not a discernible difference in the reorganization of the remaining M1 movement representations of the paretic forelimb between the two groups. However, the compensatory strategies included those that could be considered to be normal for the task, despite not being the monkeys' originally preferred strategies. It is conceivable that the neural correlates of subtler forms of compensation are nearly indistinguishable from those of recovery. The strategy described above in which macaques grasp food rewards between the fingertip and the mid-thumb rather than the thumb tip⁹⁶ could be considered a subtler form of compensation than are strategies such as using trunk movements to extend and rotate the paw (FIG. 2). The use of trunk movements to control hand position presumably involves neural changes that are quite distinct from those of the recovery of more-normal elbow and wrist movements. Nevertheless, the distinction of their mechanisms from those of training-dependent recovery has not yet received prominent research attention in animal models. One obstacle is that it is currently very challenging to precisely quantify movement patterns in manual skill tasks in rodents, which are the most popular model species for chronic stroke (BOX 2). Approaches that are in development for automated measurement of such movement patterns^{140,141} hold promise for remedying this situation.

Maladaptive compensation

It is tempting to count any means of resuming more-normal life activities after stroke as a victory, but relying on compensatory strategies can come with costs. The strategies of relying mostly on the non-paretic hand and of relying on proximal body movements instead of distal arm movements can encourage the disuse of any residual capacity for a greater range of paretic limb movements that might be achieved with practice to enable better overall functionality^{47,67,142}. Such forms of compensation could be the best option for those with the most-severe impairments; for those with milder impairments, however, they are unlikely to be. Nevertheless, even stroke survivors who have a good functional capacity in the paretic limb, as measured in the laboratory, persist in disusing the paretic limb in everyday life¹⁴³. Given that compensatory strategies that counter the remaining capacity for better overall functionality can be considered to be maladaptive, why do such strategies persist? As described next, one culprit underlying the persistence of maladaptive compensation could be the neural plasticity that is driven by it.

Neural substrates of maladaptive compensation.

Recent findings from rodent studies suggest that some of the neural changes that are driven by compensatory reliance on the non-paretic forelimb counter improvements in the function of the paretic side. This was revealed in studies that modelled the effects of learning to compensate with the non-paretic forelimb by training this limb daily in skilled reaching tasks, beginning between 4 days to 3 weeks after subtotal M1 infarcts^{11,116} (FIG. 3). Rats that received a brief (10–15-day) period of daily training of the non-paretic forelimb showed exacerbated impairments, and disuse of, the paretic forelimb^{144,145}, and diminished performance improvements in subsequent rehabilitative training of the paretic forelimb^{145–147} compared with rats that received non-training control procedures during the non-paretic limb training period. The worsening of paretic limb performance lasts for at least 2 months after non-paretic forelimb training ceases¹⁴⁸. By contrast, bilateral-reach training (that is, training of each limb in alternating trials of the same sessions) does not exacerbate impairments or diminish improvements in the performance of the paretic side¹⁴⁶.

In the absence of prior training of the non-paretic forelimb, motor skill training of the paretic forelimb improves its performance and increases its movement representation area in the peri-infarct motor cortex^{116,130–133}. Both effects are greatly reduced in animals that receive a period of non-paretic forelimb training before the onset of rehabilitative training of the paretic limb, even though the number of attempts to use the paretic limb in the rehabilitation task is not diminished¹¹⁶. Thus, a well-established correlate of improvement in the performance of the paretic side — the reorganization of movement representations — is disrupted by learning new ways of using the non-paretic forelimb, at least after strokes involving M1. It remains to be determined whether these effects generalize to other injury loci.

The effects of learning new skills with the non-paretic forelimb on the reorganization of motor maps in the peri-infarct cortex may reflect experience-dependent competition in the reorganization of synaptic connectivity in this region¹¹⁶. Motor skill training normally promotes the addition and maturation of synapses in the M1 contralateral to the trained

limb^{149–151}. The maturation of synapses is reflected by the proliferation of a mature and efficacious subtype of excitatory synapses known as perforated synapses¹⁵². Training the non-paretic forelimb also promotes synapse addition in the peri-infarct M1 but not the addition of perforated synapses. Instead, it increases the formation of synapses by multisynaptic boutons (MSBs)¹¹⁶. The presence of MSBs may reflect ongoing competition for survival between synapses¹⁵³ and, in this case, between synapses that were created in response to the experiences of the non-paretic limb versus those created in response to experiences of the paretic limb. If so, and given that callosal transections in rats attenuate the deleterious effects of training the non-paretic forelimb¹⁵⁴, it seems possible that projections from the contralesional motor cortex are a source of at least some of the competing synapses. The broader implication is that the experiences of either forelimb may ‘compete’ with one another in shaping neural reorganization patterns after stroke.

Potential clinical implications.

The findings discussed above have the disturbing implication that the neural mechanisms of improved function in the paretic side are typically subverted by the usual response to hemiparesis of learning to rely on the non-paretic upper limb. The findings also raise the possibility that analogous mechanisms of synaptic competition contribute to the persistence of suboptimal compensatory movement strategies that involve using the paretic body side. For example, an over-reliance on trunk movements to extend the arm and control hand position might shape synaptic connectivity in the motor cortex in a manner that interferes with new connections that could support a greater range of movement of the elbow and wrist. If so, given the sensitivity of neural remodelling responses to behavioural experience, it could be particularly deleterious for such strategies to be well practised in the early post-stroke period, when the neural changes can be amplified by the early pro-neuronal-growth environment.

Roles of the contralesional hemisphere

There has been much recent debate about the role of the contralesional hemisphere in functional outcome after stroke. Various clinical studies suggest that the contralesional hemisphere may contribute to function of the paretic side, or may be disruptive of this function, depending on the severity of damage to the corticospinal system, the time since stroke and other factors, as reviewed elsewhere^{113,155–159}. For example, in support of disruptive influences, the contralesional M1 can exert an excessive inhibitory influence over the ipsilesional hemisphere during paretic hand movements, as detected using paired-pulse protocols with TMS^{155,160,161}. Manipulations such as low-frequency TMS that reduce excitability or disrupt activity in the contralesional cortex improve the performance of the paretic hand in motor tasks in some patients^{155,162–164}, but there is considerable variability in this effect^{165–167}. In addition, disrupting the contralesional M1 or premotor cortex during the performance of more-complex motor tasks with the paretic hand disrupts the timing of movement with the paretic hand more so than it does in healthy controls¹⁶⁸, suggesting that the contralesional hemisphere positively contributes to paretic hand function. Similarly contradictory roles of the contralesional hemisphere can be found in the animal literature^{112,169–171}.

Contralesional contributions to re-innervation.

The contralesional motor cortex contributes to the reinnervation of regions denervated by stroke. Many studies in animal models of stroke have found that axonal projections of neurons in the contralesional motor cortex can sprout crossed collaterals to form synapses in denervated regions of the spinal cord, red nucleus, striatum, peri-infarct cortex and other regions, as recently reviewed elsewhere¹⁰⁶. This promotes the formation of new connections in regions that could give the contralesional hemisphere greater control over movements of the paretic side¹⁵⁷. Several studies in rodent models have used gain-of-function and loss-of-function manipulations that support causal relationships between sprouting from the contralesional motor cortex and improvements in motor function, including the recovery of more-normal paretic forelimb movement¹⁷² and reduced compensatory reliance on the non-paretic forelimb^{172–174}. For example, after large motor cortical infarcts, treatment with an antibody that targets the axon-growth inhibitor Nogo-A (also known as reticulon 4A) increases sprouting from the spared corticospinal tract into the denervated spinal cord, and promotes improved performance and the recovery of more-normal movements of the paretic forelimb in a skilled reaching task¹⁷². Transections of the spared corticospinal tract reinstate forepaw movement abnormalities¹⁷². Surviving cortical neurons of the injured hemisphere can also contribute to the re-innervation of the same targets^{97,98,115}. In macaques, the sprouting of ipsilesional and contralesional projections into denervated regions of the spinal cord has been found to vary depending on cortical lesion size and territory¹⁷⁵. The relative importance of the two sources of re-innervation has not been thoroughly dissected. However, some findings suggest that, given a sufficient remaining capacity for ipsilesional projections to contribute to re-innervation, the contralesional cortex may be the less relevant source of these projections for the function of the paretic limb^{97,98}.

Potential influence of compensation.

There is no debate about the role of the contralesional cortex in controlling compensatory movements, including those of the non-paretic hand and trunk. However, the possibility that its involvement in doing so could be a source of variability in how it contributes to paretic limb function has not received very much attention. Bilateral patterns of cortical functional activation¹¹³ and interhemispheric inhibition¹⁷⁶ during paretic hand movement vary with the severity of motor impairments. That behavioural experiences can influence these patterns is supported by findings that rehabilitative training of the paretic upper limb can increase the functional activation of motor regions of the ipsilesional cortex^{177,178} and reduce interhemispheric inhibition from the contralesional motor cortex¹⁷⁹. People with more-severe motor impairments rely more heavily on compensatory strategies^{42,84}. This leaves open the possibility that the experience of relying on compensatory strategies contributes to impairment-related variance in cortical activation and inhibition patterns.

As reviewed above, the use of compensatory movement strategies can influence neuroanatomical reorganization of the contralesional cortex: compensatory reliance on the non-paretic limb promotes the remodelling of dendrites and synapses in the contralesional motor cortex of rats¹²⁶. In humans after stroke, the use of compensatory shoulder abduction during simulated eating movements correlates with functional activation of contralesional cortex during these movements¹⁸⁰. This involvement of the contralesional motor cortex in

compensatory movements, and the neuroanatomical changes that result from using such movements, might alter the potential of the contralesional motor cortex to make adaptive contributions to movements of the paretic side. This possibility awaits research attention.

Perspectives and challenges

The extent of reorganization of remaining motor cortex and of its afferent and efferent projections has been strongly linked to improved functional capacity in the paretic upper limb, but these improvements can reflect recovery, compensation or both. Interventions such as motor rehabilitative training that drive motor cortical reorganization promote varying degrees of recovery of more-normal movement and more-effective compensatory movement in the paretic limb. There is not currently a clear distinction between the neural mechanisms of the recovery that can be promoted by motor rehabilitative training and those of the compensatory strategies that can be encouraged by the same training.

Compensation is often viewed as a suboptimal counterpart to recovery, but compensatory strategies for moving the paretic upper limb can contribute to improvements in its functional capacity. Nevertheless, there are more-optimal and less-optimal ways of compensating. There is clear evidence that reliance on the trunk to move the paretic arm can counter the recovery of more-normal arm movement in individuals with moderate impairments⁸³. Such compensation may be the best option after strokes that leave no remaining capacity for the recovery of more-normal movements; however, the ‘cutoff point’ for the absence of such capacity is unclear at present.

Dominant reliance on the non-paretic upper limb is a particularly troublesome compensatory strategy. It encourages the disuse of the paretic side and thus limits the return of more-functional use, through recovery or compensation. Rodent studies have found that learning new ways of using the non-paretic forelimb promotes synaptic changes that interfere, and probably compete, with the ipsilesional motor cortical changes that could otherwise contribute to functional improvements on the paretic side. This may help to explain the persistence of paretic limb disuse, even in individuals with relatively modest impairments. Encouraging damaged neural circuits to change in a manner that subserves better function on the paretic side is challenging enough. It cannot help if the same circuits have already been driven to change in a manner that impedes further change.

The important role of the contralesional hemisphere in mediating compensatory strategies is not currently a central topic in the ongoing debates about the role of the contralesional hemisphere in paretic limb function. Given the findings reviewed above, it seems reasonable to suspect that exactly how the contralesional hemisphere contributes to, or interferes with, paretic hand and arm function varies greatly depending on how involved it has already become in compensating for the loss of this function. The inter-relationship between impairment severity and reliance on compensation poses a challenge to the investigation of this possibility in clinical populations, but it is quite feasible to study through the manipulation of behavioural experiences in animal models^{101,114,115,145}.

Finally, compensation has not received the amount of consideration in animal models of CNS injury that would seem to be warranted by its reliable clinical manifestations. This effort would benefit from further refinement of measures of compensation in rodent models (BOX 2). The findings of potent and lasting influences of compensatory behavioural experiences on post-stroke brain reorganization and behavioural outcome further motivate research into compensation. They suggest that new treatments for injury-induced impairments may lie within the neural mechanisms and influences of compensatory behaviour, awaiting discovery.

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Box 1 | Recovery versus compensation

Recovery refers to the restoration of a function back to a more-normal, pre-injured state, whereas compensation refers to the substitution for, or circumvention of, impaired functions. In this Review, the term recovery describes the return of more-normal movements, and the term compensation describes the use of alternative movement strategies. The terms refer only to their behavioural-level meaning in this Review. Note, however, that in the stroke literature it is common to use the term recovery to refer to performance improvements in tasks that do not distinguish between compensation and recovery. For example, rodents are often said to recover in skilled motor tasks as measured, for example, by success rates in retrieving food rewards, despite the well-established potential for compensation to underlie these improvements^{16,69}. Behavioural compensation and recovery, as strictly defined above, often overlap in their contributions to performance improvements in such tasks.

The neural mechanisms of behavioural recovery and compensation also overlap. Stroke survivors who have sufficient remaining corticomotor function follow a ‘proportional recovery rule’; that is, their initial motor impairments improve over the first 3 months to a maximum that can be predicted on the basis of the initial impairment level¹⁸¹. The mechanisms underlying this spontaneous behavioural recovery are not well understood, but such recovery is frequently attributed to spontaneous repair and restoration at the CNS level. For example, it may involve the resolution of acute dysfunction in neural activity and cellular metabolism in regions connected to the injury site^{182,183}, the return of more-normal blood flow in peri-infarct tissue¹⁸⁴ and the reorganization of the connectivity patterns of surviving neurons¹⁰⁶.

Behavioural compensation depends, in part, on learning-related neural plasticity mechanisms¹²⁶. However, learning-related neural plasticity can depend on the sufficient resolution of neural dysfunction and on the restoration of blood flow, both of which are presumed to also be involved in behavioural recovery¹³. In addition, the resolution of neural dysfunction can depend on neural plasticity. For example, the formation of new synapses (a learning-related plasticity mechanism) contributes to the restoration of more-normal electrophysiological responses in denervated neurons¹⁸⁵.

Further complicating the matter is that some behavioural recovery is practice dependent^{73,95,96}, implicating learning-related neural plasticity as an underlying mechanism. Motor skill training even long after stroke can promote some recovery of more-normal movement^{17,83}. Practice can drive sufficient reorganization of neural connectivity in surviving brain regions to permit a degree of vicariation (take-over) of the original function of these regions^{97,186}. However, the same types of motor training can promote both recovery and compensation^{16,73,95,96}. It is likely that the distinction between the neural mechanisms of recovery and compensation is related more to the specific collection of circuits that is changed than to the general nature of the change. As a result, it could prove challenging for the neural substrates of the subtlest forms of behavioural compensation, as described in the text, to be distinguished from those of recovery. However, many of the frequently observed strategies for compensating for upper-limb hemiparesis are far from subtle (see the first four examples in TABLE 1).

These overlaps in the neural mechanisms of behavioural recovery and compensation create strong potential for their mechanisms to influence, as well as to be mistaken for, one another, thus necessitating a clear distinction between compensation and recovery at the behavioural level in research on their mechanisms.

Box 2 | Distinguishing motor recovery from compensation in rodent models

Most of the popular measures of motor function in rodent models of stroke do not distinguish between recovery and compensation. This includes grid-walking, ladder-walking and beam-walking tests, skilled reaching tests and rotarod tests, as they are normally performed. The gold standard for distinguishing motor recovery from compensation is to perform kinematic (geometry of movement) analyses^{65,68,140}, but this is currently challenging to do routinely (because the skin markers that are commonly used in kinematic systems to automatically track joint positions do not work well on rodent forelimbs). Automated measures of rodent movement that are in development^{140,141} may help to overcome this obstacle. In the meantime, there are several other ways to probe for the presence of impairments and compensation.

Alaverdashvili and Whishaw⁹³ have established qualitative measures of the movements used in reaching tasks, and these measures can be used to infer whether performance improvements reflect recovery from impairment or compensation⁹³. Some behavioural tests probe for impairments by measuring the use of compensatory strategies. The ledged tapered beam test reveals limb impairment when animals resort to stepping down to a wider ledge (compensation) as they traverse a progressively tapering beam¹⁸⁷. The Schallert cylinder test, in which the animal is placed into a transparent cylinder where they rear and support themselves with their forepaws, reveals impairment in one forelimb by measuring the compensatory reliance on the other forelimb for upright exploratory movements¹⁸⁸. Similarly, the vermicelli-handling test reveals a preferential reliance on the movements of one forepaw to move a long pasta piece into the mouth⁷¹. The contribution of the non-paretic forelimb in performance improvements can also be probed by retesting the animals after this limb has been constrained¹⁶ or peripherally anaesthetized^{128,189}. For example, if peripheral anaesthetization of the non-paretic forelimb reinstates impairments of the paretic limb in a grid-walking task, whereas the same manipulation in intact animals has little effect, the pre-anaesthetization performance improvements are inferred to be dependent on the non-paretic limb and thus compensatory.

Callosotomy

The surgical procedure of severing the corpus callosum at the midline.

Non-paretic

Refers to the side of the body that is ipsilateral to the stroke.

Paretic

Showing weakness, ineptitude and partial loss of voluntary movement. Usually most severe on the side of the body that is contralateral to the stroke.

Rehabilitation

A treatment designed to improve functional capacities. It includes physical therapy for motor impairments.

Precision grip

Grasp between the tips of the thumb and a finger.

Motor skill learning

The practice-dependent refinement of novel movement sequences.

Action Research Arm Test

A test that measures the ability to perform various actions with the paretic upper limb, such as grasping differently sized objects and pouring water from a glass.

Homotopic

Describes an anatomical region corresponding to that of the other hemisphere or body side.

Movement representations

The territories in the motor cortex that control discrete movements, such as of the wrist or of a digit. They are usually defined on the basis of movements evoked by electrical stimulation and are also known as a 'motor map'.

Perforated synapses

Synapses with discontinuous postsynaptic densities that are on average larger and more potent in evoking postsynaptic depolarizations than are other synapses.

Multisynaptic boutons (MSBs).

Single boutons that form synapses with more than one postsynaptic dendritic surface.

Paired-pulse protocols

Tests for the facilitation or depression of a stimulation-evoked neural response due to a preceding stimulation.

Crossed collaterals

Branches of an axon that cross the midline to terminate in the hemisphere opposite to that of the originating axon.

Figure 1 | The motor cortex and its descending projection pathways are often affected by strokes that result in upper-extremity impairments.

a | Simplified illustrations of motor cortical regions of a human (left), and of motor cortical regions of a naive rat, derived using intracortical microstimulation (right), are shown. The colours show the cortical territories that are responsible for the movement of different body parts. The motor cortical control of the upper limbs is mostly crossed, such that the left hemisphere controls movement of the right side and vice versa. **b** | Occlusions or ruptures in the cerebral vasculature (red) that supplies motor cortical regions (the distal middle cerebral artery) and its projection pathways (for example, the anterior choroidal and striate arteries) position strokes (the dark grey regions on the rat coronal sections on the right) that either kill the cortical neurons that control upper-limb movement or disconnect their projections to the spinal cord and other subcortical structures, such as the red nucleus and reticular formation. The degree of disruption of the descending motor cortical pathway due to either cortical or subcortical strokes predicts the severity of motor impairment^{18–20}. The colours of the corticospinal neurons correspond to the body parts that they control as in the motor cortical regions in part **a**. The rat coronal sections show the locations of ischaemic infarcts that have been used to model post-stroke upper-extremity impairments; these infarcts are located in

the forelimb region of the primary motor cortex^{69,73} (M1; which is supplied by the distal middle cerebral artery) and in the posterior limb of internal capsule^{77,190} (which is supplied by the anterior choroidal artery). The dashed lines indicate the disconnection of descending cortical projections.

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Figure 2 | Illustrations of compensatory movement strategies for upper-limb hemiparesis.

a | The illustration shows typical reach and grasp movements in healthy humans. **b** | When reaching with the paretic upper limb after stroke, forward trunk and shoulder displacement and rotation compensate for the diminished control of more-distal movements^{46,47}. If not instructed otherwise, the non-paretic side often assists movements of the paretic side. **c** | More commonly, the non-paretic side is used for unimanual tasks^{54,55}. **d** | The illustration shows typical movements used by healthy rats to reach for and consume a palatable food pellet (green sphere) in an apparatus that forces the use of one forelimb (that is, an inner chamber wall placed close to the reaching window on the side of the trained limb blocks the body position needed to reach the pellet with the other forelimb). An alternative method is to place bracelets on the wrist of the other forelimb that prevent its extension through the reaching window⁸² (not shown)). **e** | After unilateral motor system injury, rats perform reaching tasks with the paretic forelimb using compensatory movements of the trunk, head and non-paretic forelimb^{13,16,63}. This includes the use of trunk rotation to control paretic paw position (left) and greater head movement (right) to bring the mouth to the paretic paw (rather than the paw to the mouth). The paw orientation is suboptimal for grasping the pellet. **f** | The non-paretic forelimb is often used to assist in paretic limb movements.

Figure 3 | Different trajectories of cortical reorganization depending on forelimb behavioural experiences after motor cortical infarcts in rodent models.

Rodents in a standard laboratory cage have limited opportunity to practice fine motor skills with the forelimbs, affording a strong degree of experimental control over these experiences.

a | In the absence of interventions, increased reliance on the non-paretic forelimb for movements in the home cage (known as unskilled compensation) promotes synapse addition and selective synapse maturation in the contralesional primary motor cortex (M1)¹²⁶. These changes in the contralesional cortex have no known functional relevance for the paretic limb.

b | The changes in the contralesional cortex are amplified if animals are trained with the non-paretic forelimb on a skilled reaching task that is novel for this limb¹²⁹. The same training worsens impairment severity in the paretic forelimb¹⁴⁵. **c** | Rehabilitative training of the paretic forelimb in a skilled reaching task promotes the maintenance and re-emergence of the remaining forelimb motor maps in the peri-infarct M1 and improves paretic limb reaching performance^{131,132}. The performance improvements can reflect the recovery of more-normal movements, the refinement of compensatory movements or both¹⁶. **d** | The performance improvements and forelimb motor map maintenance that result from rehabilitative training are diminished as a result of prior skill learning with the non-paretic forelimb¹¹⁶. This is associated with the addition of multisynaptic boutons (MSBs) in the peri-infarct M1, which may reflect competitive influences of the two limbs on synapse addition and maturation in the peri-infarct cortex. The motor cortical map illustrations on the top and bottom-right brains are adapted with permission from REF. 116, Society for Neuroscience.

Table 1

Examples of compensatory movement strategies for upper-limb hemiparesis

Normal strategy	Compensatory strategy	Type of study	Refs
Use of both hands together	Dominant reliance on the non-paretic hand	Clinical	7–9, 54–57
		Rodent	70–72
Hand extended via elbow extension	Hand extended via trunk displacement	Clinical	25,42,43
Hand oriented via wrist movements	Hand oriented via trunk rotation	Clinical	46,47
		Rodent	63,69
Palm to mouth via wrist supination	Palm to mouth via trunk and head rotation	Rodent	16,63,69
Scaling of finger opening to object size	Excess finger opening to grasp	Clinical	31,52,53
Grip force varied with object properties	Excessive grip force	Clinical	31,53
Grasp via flexion at distal, and extension at proximal, finger joints	Grasp via flexion at proximal finger joints	Clinical	51
Precision grip	Grasp between fingertip and palm or proximal thumb	Monkey	75,76,96