

Mechanisms underlying recovery of motor function after stroke

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Neurological damage, and stroke in particular, is the leading cause of long term disability worldwide. There is growing interest in the part that central nervous system reorganisation plays in recovery of function. Techniques such as functional magnetic resonance imaging and transcranial magnetic stimulation permit the non-invasive study of the working human brain, and suggest that functionally relevant adaptive changes occur in the human brain after focal damage. An understanding of how these changes are related to recovery will facilitate the development of novel therapeutic techniques that are based on neurobiological principles and that are designed to minimise impairment in appropriately targeted patients suffering from stroke.

work in animal models has clearly shown that the molecular and cellular substrates of plasticity are changed in both perilesional and distant brain regions.⁶ Developmental proteins not normally expressed in the adult brain re-emerge in the hours and days after focal brain injury and exert their effects for a number of weeks or months.⁷ These proteins are involved in neuronal growth, apoptosis, angiogenesis, and cellular differentiation. Structural changes have also been seen, with evidence of increased dendritic branching⁸ and synaptogenesis.⁹ There is also evidence of reduced GABAergic inhibition and increased hyperexcitability in both perilesional and distant cortex after focal injury.¹⁰ This finding is of particular interest as it is easier to induce long term potentiation, long considered a key substrate of learning, under such conditions.^{11 12}

In the UK, neurological damage, and in particular stroke, accounts for about 40% of severely disabled people.¹ The management of complex disability currently relies on rehabilitation and there is little doubt that the overall approach is effective. Stroke unit care, for example, reduces death, institutionalised care, and dependency at one year² and also in the long term.³ However, while the value of specific rehabilitation therapies aimed at assisting adaptation to impairment is well recognised, strategies designed to reduce impairment are perhaps less well developed.⁴ Recent advances in the understanding of the mechanisms of neurological impairment suggest that the study of whether, and particularly how treatments can reduce impairments and by implication long term disability may be fruitful.⁴ This is an approach to which the clinical neurosciences can make a unique contribution.

Taken together, these changes suggest that the damaged brain is more amenable to activity driven changes in structure and consequently function. In other words it is more plastic. Similar injury induced changes are likely to occur in the human brain, and manipulation of these processes might provide a means of maximising the recovery potential in patients with focal brain damage. Research in humans is performed largely at the systems level using techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), which permit measurement of task related brain activation with excellent spatial resolution, and transcranial magnetic stimulation (TMS), a safe, non-invasive way to excite or inhibit the human cortex with high temporal resolution. Guidelines for the use of functional imaging in particular, as a tool for studying recovery from stroke have recently been published.¹³

One of the commonest impairments after stroke is hemiparesis. This review will discuss the current level of understanding of how the brain responds to focal brain injury, and in particular stroke, in a way that might facilitate recovery of motor function, and how this is beginning to inform novel treatments.

HOW DOES THE HUMAN BRAIN RESPOND TO FOCAL INJURY?

Until recently there has been surprisingly little evidence that reorganisation in the human brain mediates recovery from hemiparesis after stroke. Hemiparesis is a consequence of the interruption of motor signals that pass via the corticospinal tract to the spinal cord motor neurons. Fibres in the corticospinal tract originate mainly from the primary motor cortex (known as M1). However,

THE BRAIN AS A PLASTIC STRUCTURE

Experiments in both animals and humans show that some regions in the normal adult brain, particularly the cortex, have the capacity to change structure and consequently function during learning or in response to exposure to enriched environments.⁵ This process is often referred to as plasticity. After focal brain damage,

Abbreviations: fMRI, functional magnetic resonance imaging; TMS, transcranial magnetic stimulation; PET, positron emission tomography; sMA, supplementary motor area; CMA, cingulate motor area; PMd, dorsolateral premotor cortex

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there are also contributions from other motor related brain regions such as dorsolateral premotor cortex (PMd), supplementary motor area (SMA), and cingulate motor areas (CMA), together considered to be the secondary motor areas. Primary sensory cortex, some parts of parietal cortex, and insula cortex also contribute to the corticospinal tract, hinting at the necessary integration of motor and sensory functions for successful motor performance. Functional imaging permits the investigation of which brain regions are active during the performance of a motor task, in both healthy controls and stroke patients. Studies in primates have shown that these regions not only have projections to spinal cord motor neurons, but also to M1. It was suggested that in the face of brain damage resulting in the reduction of motor signals from M1, that output from these other contributors to the corticospinal tract, particularly the secondary motor areas, might compensate.¹⁴ Early functional imaging studies did indeed report greater activation in a number of motor related brain regions in recovered long term stroke patients compared with control subjects.¹⁵ However, a clear relation between motor related brain activation patterns and outcome in chronic subcortical stroke has only recently been found.¹⁶ A group of patients with infarcts sparing primary motor cortex were studied. Outcome among the group ranged from those who had recovered all pre-stroke function to those who were dependent, unable to walk, with minimal recovery of finger flexion in the upper limb. During the performance of a simple repetitive hand grip task those with poorer outcome recruited more of the primary and secondary motor systems in both affected and unaffected hemispheres. Patients with the best outcome had a “normal” activation pattern when compared with normal controls. This result does not immediately support the role of secondary motor regions, such as dorsolateral premotor cortex (PMd), supplementary motor area (SMA), and cingulate motor areas (CMA) in the recovery process. However, long term motor outcome is strongly influenced by the integrity of the corticospinal tract.¹⁷ In the face of damage to the primary motor output system, it is probable that recruitment of secondary motor regions might occur, as SMA, PMd, and CMA each has projections to spinal cord as well as to primary motor cortex (M1) and so might be useful in trying to generate some form of motor output. These projections are unlikely to completely substitute for projections from M1 as they are less numerous and less efficient at exciting spinal cord motor neurons.¹⁸ However, it is unlikely that the response to focal injury entails the simple substitution of one cortical region for another. Nodes within the remaining network may take on new roles. For example, the premotor cortex seems to adopt some of the functional characteristics of the primary motor cortex after subcortical stroke.¹⁶ This is seen predominantly in those patients with poorer outcome, and presumably reflects a changing role for premotor cortex when motor output from primary motor cortex is interrupted.

Key points (1)

- Stroke is a major cause of disability, the treatment of which is based on a rehabilitative approach.
- Rehabilitation treatments seek to improve function by adaptation to impairment or minimising impairment.
- The latter approach is not well developed, but advances in the understanding of the mechanisms of impairment and recovery will encourage the development of new treatments designed to minimise impairment.

But are these regions truly contributing to recovery? Increased activity in ipsilesional (contralateral to the affected hand) PMd has been associated with therapy induced improvement in both upper limb¹⁹ and gait²⁰ function. One experimental approach is to disrupt the function of a region thought to be contributing to recovery, and observe whether the “recovered” motor function is affected. Transcranial magnetic stimulation (TMS) delivers magnetic pulses to the cortex, which has the effect of temporarily disrupting local cortical function. Disruption of ipsilesional PMd²¹ as well as contralesional (ipsilateral to the affected hand) PMd²² using TMS impairs performance of a simple motor task in long term stroke patients but not controls. This is highly suggestive that these regions are functionally useful. However, TMS to ipsilesional PMd is more disruptive in those patients with less impairment²¹ and TMS to contralesional PMd is more disruptive in patients with greater impairment,²² showing that PMd in the unaffected hemisphere may be called upon more so in those with poorer outcome—that is, those with the greatest need.

An intact ipsilesional M1 is clearly beneficial for recovery,²³ but the role of M1 in the unaffected hemisphere remains controversial. Several functional imaging studies have reported task related activation of contralesional M1 in long term stroke patients,¹⁵ particularly in the posterior part of M1 that was activated more so by those patients with poorer outcome.¹⁶ In studies with human stroke patients, disruption of contralesional M1 function by TMS has not impaired performance in simple motor tasks, calling into question the functional significance of increased contralesional M1 activation after stroke.^{22, 23} Rather than contributing towards recovery, it has recently been suggested that contralesional M1 may impair recovering motor function in patients with subcortical stroke by exerting an abnormally high degree of interhemispheric inhibitory drive towards ipsilesional M1 during attempted voluntary movement of the affected hand.²⁴

Thus in the chronic stroke brain, there is a new functional cerebral architecture, one that is not as effective as that in the intact brain, but that nevertheless will attempt to generate some form of motor signal to spinal cord motor neurons in the most efficient way. The exact configuration of this new functional architecture will be determined by a number of factors, not least the exact anatomy of the damage and the changed way in which remaining cerebral structures might interact with one another (for example, changes in the interhemispheric relation between primary motor cortex of affected hemisphere and unaffected hemisphere), but also the biological age of the subject, and the premorbid state of their brain, both of which will influence the potential for plastic change, either lesion induced or therapeutically driven.

Studies in long term stroke patients do not tell us how this reorganised state evolved. Longitudinal fMRI studies of similar patients show an initial overactivation in many primary and non-primary motor regions.^{25–28} This overactivation, which is present in both hemispheres, is more extensive

Key points (2)

- Molecular and cellular changes occur in the brain soon after damage that suggest it is more amenable to activity driven reorganisation, thus providing the substrate for recovery.
- These processes can be studied in the working human brain with functional magnetic resonance imaging and transcranial magnetic stimulation.

in those with greater motor impairment. Thereafter any functional recovery is associated with a focusing of brain activation patterns towards that seen in controls.²⁸ This focusing is similar to that seen in the normal brain during motor skill learning.²⁹ However, although it is unsurprising that the damaged brain will attempt to use highly preserved neural systems such as those subserving motor skill learning to maximise functional motor recovery, the degree to which this is successful will depend on the integrity of such networks.

THERAPEUTICALLY DRIVEN CHANGES IN BRAIN FUNCTION

It is clear that functionally relevant adaptive changes take place in the human brain after focal injury. But what drives these changes? Can we take advantage of them to treat impairment? The key lesson from animal models of focal damage is that manipulation of environmental, behavioural, or pharmacological context does not have an effect on recovery on its own, rather it can influence the effect of a specific therapy. In other words some techniques seem to “condition” the brain, so that it is temporarily more responsive to afferent input, and the best chance of driving cerebral reorganisation and functional recovery occurs when the brain is most receptive to afferent signals.

It is probable that these optimal conditions are present only in the first few months after stroke. As described, there are a number of early changes at the molecular and cellular level that increase the potential for activity driven change in neural circuits in the damaged brain. Practice of a motor task for example may be more effective at using the (surviving) neural machinery that subserves motor learning when areas of the cortex are hyperexcitable. Data from both animal and human studies show that many of these changes, including hyperexcitability, diminish after a few months.^{7 30–32} Thus the therapeutic window of opportunity seems to be limited.

However, it has long been seen that functional gains can be made even in the chronic stage after stroke. As a result, there is current interest in increasing the potential for activity driven cerebral reorganisation in the chronic phase after stroke, once the early changes such as hyperexcitability have disappeared. This might allow therapeutic input, for example, targeted physical therapy, to have an increased effect. From our knowledge of how the brain responds to focal injury and how this relates to recovery it should be possible to generate hypothesis driven approaches to neurorehabilitation. One such approach recognises that the balance of transcallosal inhibitory activity between the affected and unaffected motor cortices may be important in achieving the optimal functional motor outcome. Thus increasing the excitability of affected hemisphere M1 by means of repetitive TMS as a means of “conditioning” the brain to be more responsive during therapy is an example of an interesting theoretically driven approach to the treatment of motor impairment.^{33 34} Indeed, some investigators are going further and are investigating the

Key points (3)

- Functionally relevant reorganisation occurs in the human brain after stroke.
- Secondary motor areas become increasingly functionally relevant with greater damage to the primary motor system.
- However, secondary motor areas are unlikely to be able to completely substitute for the actions of the primary motor system

Key points (4)

- Some drugs, for example, amphetamine, and repetitive transcranial stimulation may increase the effect of motor practice during a physiotherapy if given just before a treatment session

safety and efficacy of placement of epidural electrodes over affected hemisphere motor cortex in a long term stroke patient for the purpose of subthreshold electrical stimulation.³⁵ As an alternative it has been hypothesised that because of the potential inhibitory effect of contralesional motor cortex on ipsilesional motor cortex in chronic stroke patients,²⁴ attempts to reduce this inhibitory drive by directly targeting the unaffected hemisphere might lead to some benefits.

The balance of interhemispheric inhibitory drive can also be manipulated by changing somatosensory feedback from the limbs. Reducing somatosensory input from the unaffected hand can lead to improvements in motor performance in the non-anaesthetised affected hand that briefly outlast the duration of the anaesthesia.³⁶ Immobilising the unaffected hand to encourage use of the affected hand (a technique known as constraint induced movement therapy)³⁷ may also reduce somatosensory input from the unaffected hand. This might account for some of the benefit reported with constraint induced movement therapy based techniques.³⁷ Conversely, increasing somatosensory input from the affected hand using median nerve stimulation has been shown to improve motor function in a small number of long term stroke patients.³⁸ These small scale proof of principle studies suggest that such theoretically driven approaches are worth pursuing.

Recovery processes might also be influenced by pharmacological treatments that modulate various neurotransmitter systems.^{39 40} Some drugs might have beneficial effects if given before physiotherapy by conditioning the brain to be more responsive during therapy, as proposed for repetitive TMS. Agents such as amphetamine⁴¹ and l-dopa⁴² have been used with interesting results, although the mechanisms by which

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these drugs exert such an effect is far from clear. For example, amphetamine seems to facilitate the induction of activity driven long term potentiation in cortex,⁴³ and is also likely to have an alerting effect. It is possible to see how both of these could act to increase the effect of motor practice for example. If these treatments are to be effectively targeted, a greater understanding of how and in whom they exert their effects is required.

Can functional imaging studies be used as surrogate markers of recovery? Recent studies have shown changes in brain activation patterns after therapy targeted at specific impairments, for example, constraint induced therapy. In the motor domain there seem to be increases in motor task related activation in the affected hemisphere (for example, in M1 or PMd) and reduced activation in the unaffected hemisphere after a period of treatment.^{19 20 44-46} These studies are interesting in that changes in cerebral organisation can be linked to reductions in impairment. However, these changes are unlikely to be specific for a given type of treatment, and so do not help us to understand the mechanism of action of that treatment. Further experiments that test the effects of treatments on particular aspects of brain function in different patient groups may help in this respect. Such approaches may allow treatments to be targeted at suitable patients. Thus rather than act as markers of recovery, it is more likely that functional imaging studies will help to show which types of treatments should be given to different subtypes of stroke patients and when. For example, it has recently been suggested that modulating attention towards a motor task may be more or less beneficial depending on the chronicity of the stroke.⁴⁷

In summary, advances in the neurosciences are leading to a greater understanding of the mechanisms of recovery after stroke. Focal brain damage results in a new functional architecture that is dependent on the anatomy of the damage, the time since the damage, the biological age of the patient, and lastly the amount of therapy already received. It is probable that the effect of a particular treatment or intervention in any given person will depend on these factors. Thus further research will not only provide a basis for novel and rational strategies aimed at reducing impairments after stroke and other neurological conditions, but will enable these treatments to be appropriately targeted.

QUESTIONS (TRUE (T)/ FALSE (F); ANSWERS AT END OF REFERENCES)

1. Rehabilitation treatments are designed primarily to assist adaptation to impairment
2. Molecular and cellular changes can be seen in the adult brain early after damage that are normally seen only in the developing brain
3. Drugs such as amphetamine may promote recovery of motor or language functions if given regularly after stroke
4. Full recovery of hand motor function can occur when secondary motor areas such as premotor cortex and supplementary motor area take over function of damaged brain regions.
5. Repetitive transcranial magnetic stimulation may improve the effect of targeted physiotherapy if delivered just before a treatment session.

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ANSWERS

1. False. Although approaches that assist adaptation to impairment are well developed, treatments aimed at minimising impairment are a key part of the rehabilitation process.
2. True. Such changes are reported in animal models of focal brain injury and seem to last for a few months. Furthermore, these changes suggest that the damaged brain may respond in the same way as the developing brain to environmental stimulation
3. False. Drugs such as amphetamine might increase the effect of targeted physiotherapy or language therapy only if given just before the treatment session.
4. False. Although recruitment of these brain regions after stroke is likely to be functionally useful, because of the nature of the projections from these regions to spinal cord motor neurons, they are unlikely to support complete recovery of function.
5. True. Repetitive transcranial magnetic stimulation to an intact motor cortex in the affected hemisphere might increase the effect of subsequent physiotherapy.