

Plasticity and its Role in Neurological Diseases of the Adult Nervous System

Recovery after acute neurological damage, e.g. stroke¹ (Table 1), is believed to involve reorganisation of neural circuitry, which enables non-damaged parts of the brain to appropriate new functions. A pragmatist might reasonably argue that understanding the mechanisms underpinning plasticity is not necessary; the goal for physicians is simply to maximise plasticity and, thereby, speed recovery. However, this simple strategy may not work. Excessive or aberrant plasticity has been proposed to cause diseases (Table 1). Therefore, harnessing plasticity for therapeutic benefit requires an understanding of the process of cortical reorganisation and the underlying cellular mechanisms.

Plasticity is greatest in the CNS during developmental 'critical periods',^{2,3} but the capacity for significant plasticity remains in adulthood.^{4,5} This article focuses on our understanding of plasticity in adolescent and adult cortex. We discuss the role of plasticity in disease and consider approaches that may be used to enhance or reactivate plasticity.

Table 1: Neurological conditions in which plasticity may play a role

Recovery or amelioration of CNS disease	Maladaptive plasticity
Stroke	Phantom limb pain
Multiple sclerosis	Complex regional pain syndrome type 1
Alzheimer's disease	Focal dystonia
Huntington's disease	Tinnitus
Brain tumours	Post-traumatic epilepsy

Mechanisms underpinning reorganisation

Cortical reorganisation during learning or as a result of disease can be best thought of as a process that involves early functional modifications followed by structural changes that consolidate functional reorganisation (Table 2). Functional modifications typically comprise alterations in synaptic strength possibly due to long-term potentiation or long-term depression.^{6,7} The ensuing structural changes have been described on multiple spatial scales. The most subtle structural changes occur at existing connections between neurons. The shape of dendritic spines, which form the postsynaptic component of excitatory synapses, may alter with modifications in synaptic strength. Strengthening or weakening of connections can be stored as changes in the number of synapses forming those connections. In contrast, formation of new connections may involve axonal growth and/or dendritic remodelling, which are commonly subsumed under the title 'rewiring'.⁸ Large-scale rewiring has been described after damage to the nervous system,⁹ but there is limited evidence that it occurs to a marked extent when the nervous system is intact.¹⁰ The difference in propensity for rewiring

may simply be one of degree, i.e. nervous system damage induces a more complete alteration in inputs compared with learning, or damage may enable activation of new mechanisms. Finally, neural circuits may remodel as a result of implantation of stem cells into the CNS or incorporation of new neurons following adult neurogenesis.¹¹

Space restrictions mean that we cannot describe the role of plasticity in all of the conditions listed in Table 1. Instead, we briefly discuss stroke as an example of acute neurological damage and consider how plasticity may ameliorate symptomatic deterioration in Alzheimer's disease (AD).

The role of plasticity in recovery from stroke

Plasticity has been implicated in the recovery from acute brain damage.¹ Reorganisation occurs in both the perilesional cortex and in cortex distant from the stroke.¹² Structural changes provide a substrate for substantial plasticity. In vivo two-photon imaging of the dendrites of excitatory neurons reveals a dramatic increase in dendritic spine formation, which peaks 1-2 weeks after lesion, and is specific to the peri-infarct region.¹³ Axonal sprouting can occur both within perilesional cortex¹⁴ and over greater distances. Following ischaemic injury to the hand area of primary motor cortex (M1) in squirrel monkeys, axons originating in ventral premotor cortex that normally innervate M1 exhibited sharp changes in trajectory near the lesion site, and formed a novel projection to hand areas of primary somatosensory cortex.¹⁵ However, not all reorganisation is beneficial. For example, persistent reorganisation in contralateral premotor areas following M1 lesions correlates with poor recovery.¹²

Plasticity and amelioration of Alzheimer's disease (AD)

A role for plasticity in neurodegenerative conditions may not be obvious at first glance. The pathological hallmarks of AD are amyloid plaques, neurofibrillary tangles and neuronal loss. However, loss of synapses in the hippocampus and neocortex correlates far better with cognitive decline than do the appearance of plaques or tangles.¹⁶ Intriguingly, pathological changes begin in those brain areas with the greatest capacity for plasticity. These findings suggest that AD is primarily a disorder of synapses.¹⁷

There is considerable debate surrounding the molecular mechanisms underlying synaptic dysfunction in AD. It is thought that abnormal protein aggregates and/or their soluble counterparts disrupt plasticity multifariously. Whatever the mechanism(s), the outcome of synaptic dysfunction is that neurons and the circuits that they form are unable to respond to environmental changes or to store new information. Treatment strategies may, therefore, be based on enhancement of plasticity to compensate, at least in part, for the synapses that have been lost. Alternatively, approaches to reduce synaptic dysfunction by attacking the disease itself might be adopted.



Claire Cheetham is a King's Medical Research Trust PhD student studying the mechanisms underlying plasticity of local excitatory circuitry in rodent barrel cortex at the MRC Centre for Neurodegeneration Research, King's College London. Her undergraduate training was at Imperial College London.



Gerald Finnerty is a Wellcome Trust Senior Fellow in the Clinical Sciences, Principal Investigator at the MRC Centre for Neurodegeneration Research, King's College London and Honorary Consultant Neurologist at King's College Hospital. His major interests concern the role of experience-dependent plasticity during learning and in diseases of the brain.

Correspondence to:
MRC Centre for Neurodegeneration Research,
King's College London,
DeCrespigny Park,
London, SE5 8AF, UK.
E. g.finnerty@iop.kcl.ac.uk

Level of structural change



Table 2. Mechanisms involved in adult plasticity

	Presynaptic	Postsynaptic	Effect
Synaptic function	Altered probability of release	Changes in receptor numbers and/or properties	Altered synaptic strength
Synaptic structure	Formation/loss of axonal boutons	Formation/loss of dendritic spines	Modifies synapse number
Neuronal Wiring	Axonal growth or altered arbourisation	Dendritic growth or retraction	Rewiring of neuronal connections
Neurogenesis	Stem/progenitor cells e.g. from subventricular zone or hippocampal dentate gyrus		Incorporation of new neurons into circuits

Therapeutic strategies

Experimental studies are now leading to the development of novel therapeutic strategies for disorders of the nervous system. For example, studies on the recovery of motor function following forelimb deafferentation in monkeys have led to the development of constraint-induced movement therapy. This treatment aims to reverse the phenomenon of 'learned non-use',¹⁸ and involves restricting movement of the normal limb combined with intensive training of the paretic limb. Similar strategies have been applied to the chronic motor symptoms of stroke in humans and have led to significantly increased function of the affected arm that persists for at least two years.¹⁸

Enhancement of plasticity during recovery periods may be an attainable goal. Some of the factors involved in closure of developmental critical periods are known and these may contribute to the lower levels of plasticity exhibited in mature cortex. Formation of the extracellular matrix¹⁹ and myelination²⁰ are required for critical period closure in visual cortex. Enzymatic degradation of chondroitin sulphate proteoglycans in the visual cortex of adult animals results in reactivation of ocular dominance plasticity.¹⁹ Axonal regeneration following brain damage is restricted by myelin-associated proteins, which signal via the Nogo-66 receptor (NgR), thereby reducing functional recovery.²⁰ Therefore, temporary inactivation

of NgR signalling in targeted brain areas could help to boost plasticity.

Transplantation of progenitor cells is a promising strategy for the replacement of damaged neurons and/or glia. However, progenitor cells may also enhance plasticity by mechanisms other than their incorporation into neural circuits.²¹ For example, retinal progenitor cells secrete matrix metalloproteinase-2, which promotes neurite outgrowth by proteolysis of outgrowth inhibitors.²² However, treatment strategies that provide a permissive environment for axonal growth and dendritic remodelling are not sufficient to ensure recovery. The factors that regulate formation of functional neural circuits in adult cortex need to be understood, particularly if maladaptive plasticity and its associated diseases are to be avoided.

Conclusion

Basic science has suggested new therapeutic strategies for treating brain disorders based on harnessing experience-dependent plasticity. Further advances are required before translation to the bedside becomes a reality. In particular, a more detailed understanding of the cellular mechanisms underlying cortical reorganisation is required to maximise benefit while minimising the risk of iatrogenic disease. However, the foundation is being laid for a new generation of treatments that will reduce the burden imposed by neurological diseases.

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