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Neuroplasticity and brain repair after stroke

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Purpose of review

This review considers recent insights into the neurobiology of repair after stroke in animals and humans, the range of emerging therapies to promote repair and recovery after the acute phase of stroke, and issues related to optimizing trials of such therapies.

Recent findings

Animal studies continue to shed light on the molecular, vascular, glial, neuronal, behavioral, and environmental events that are important to the spontaneous behavioral recovery that is observed during the weeks after a stroke. Animal and human studies are examining a wide range of potential interventions that may favorably modify outcome, including small molecules, growth factors, cell-based approaches, electromagnetic stimulation, a range of devices and robots, and intense physiotherapy methods, including constraint-induced movement therapy. Optimal prescription of these restorative therapies in human patients with stroke requires further study, including defining potential roles for functional neuroimaging.

Summary

A wide range of therapies shows promise for improving poststroke brain repair. Insights into the neurobiology of brain repair after stroke in animals and in humans continue to accrue. This information might prove useful in designing and implementing clinical trials that aim to measure the clinical effects of restorative therapies after stroke.

Keywords

plasticity, recovery, stem cells, stroke, therapy

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Introduction

Stroke remains a leading cause of death and disability in the USA and many other countries. It can cause deficits in a number of neurologic domains, most commonly in the motor system [1]. In most patients some degree of spontaneous behavioral recovery is observed during the weeks to months after stroke onset [2,3]. This recovery is generally incomplete, however. A key challenge is to elucidate the mechanisms of spontaneous behavioral recovery after stroke, and to use this information to guide optimal prescription of restorative therapeutics after stroke.

Clinical studies of the natural history of behavioral recovery after stroke show divergent patterns across different domains of neurologic function. Nakayama *et al.* [2] found that maximum arm motor function was achieved by 95% of patients within 9 weeks. Pedersen *et al.* [4] found that final level of language function was achieved in 95% of patients by 6 weeks poststroke. Hier *et al.* [5] also found that recovery from neglect was largely complete by 3 months. One pattern across these and other studies is that individuals with more severe deficits recover over a longer time period.

Animal studies have provided clues to a number of the key molecular events that are important to spontaneous recovery after stroke [6–8,9•,10]. Direct measure of these molecular events is generally not possible in humans. Brain mapping can be used to derive insights into the basis of spontaneous recovery after stroke in humans, however, and many results have been concordant with findings in animals. Recent reviews have considered this issue [11–13].

A critical determinant of behavioral outcome in humans is the function of elegant and eloquent neocortical areas that, at prestroke baseline, are central to generation of behaviors such as movement, language, and attention. The extent to which these areas are injured and exhibit reduced function has a primary influence on behavioral outcome [14,15•]. Probing the function of primary neocortex after stroke is complicated by the difficulty of disentangling the effects of injury from plasticity. Depending on the topography of injury, the location of cortical function can be displaced to neighboring areas [16,17], a process that arises independently of other poststroke plasticity events such as change in inter-hemispheric balance [18]. Other studies have found

that the topography of stroke injury influences functional reorganization after stroke [19]. Regional changes in brain function after stroke can have anatomic correlates such as increased cortical thickness [20].

Although activation in the peri-infarct zone has been specifically noted [21–23], its behavioral significance remains to be fully clarified. One recent functional magnetic resonance imaging (fMRI) study of patients with cortical stroke did not identify a significant correlation between extent of peri-infarct activation and behavioral outcome after stroke [24]. This assessment was complicated, however, by the additional observation that the T2*-weighted MRI signal used to measure brain activation with fMRI was itself altered in the peri-infarct zone, perhaps because of glial scarring.

Increased activation within multiple nodes of secondary, association cortex that together comprise a distributed network is a common poststroke activation pattern [17,21,25–27], described in brain networks related to a range of neurologic domains including motor, language, and attention functions. Maintenance of behavioral output after injury to one node of a network is associated with increased activation within surviving network areas. This extends to the contralesional hemisphere, where increased recruitment after stroke is seen and can be quantitated via a laterality index [21], methods for which have been refined [28]. Such increases in activation are greatest in those with the poorest behavioral outcome or largest lesions [18,28–30].

Recent observations related to spontaneous recovery in animals

Recent studies have substantiated that spontaneous behavioral recovery after unilateral infarct occurs on the basis of a wide range of bilateral growth-related brain events. These include axonal, dendritic, and synaptic changes; increased activation and migration of endogenous neural stems; and changes in glia, inflammation, and angiogenesis [7,9•,10]. In many cases, a better understanding of these processes might assist in defining therapeutic targets for improving poststroke brain repair in humans via pharmacologic [31–36], cell-based [37,38], immune-based [39,40], gene transfer [41], and physical [42] therapeutic approaches. A number of factors can influence these repair-related events, such as infarct size or degree of environmental enrichment [43]. Dancause *et al.* [44] described a specific form of neuroanatomic reorganization distant from infarct, whereby primates with primary motor cortex injury produce a novel projection from ventral premotor cortex to somatosensory cortex; this model of poststroke remodeling might prove particularly instructive.

MRI studies have also been instructive. van der Zijden *et al.* [45] used MRI to measure changes in brain region connectivity in rats subjected to occlusion of the middle cerebral artery. This is of particular importance because, as with previous work from this laboratory on fMRI in rats with experimental stroke [46], the MRI investigational approach is similar to that used in humans. Therefore, the potential for direct comparison and translation to the human experience is high.

Recent observations related to spontaneous recovery in humans

Numerous profound changes evolve in the brain during the early days after stroke [47]. Significant changes in organization of brain function can arise as late as 12 months after stroke, however [48]. Despite this wide range, Woldag *et al.* [49] found that day 7 clinical assessments have the strongest predictive value for final behavioral outcome.

The influences that drive poststroke repair continue to be clarified. The degree of vascular insult needed to incite repair-related reorganization might be much lower than was previously appreciated [50]. The specific tracts injured by stroke could be important to elucidating patterns of deficits, plasticity, and treatment response [19,51,52••]. Ward *et al.* [53], in a study of eight patients, found that a compensatory increase in regional fMRI activation within several bilateral brain areas, including both primary and secondary motor cortices, was linearly related to the degree of reduction in transcranial magnetic stimulation (TMS) measures of motor cortex/corticospinal tract functional integrity. Studies have confirmed that inhibition of the ipsilesional hemisphere by the contralesional hemisphere – a potentially important process whose modulation might be useful for improving cortical output – can be increased after stroke [54], although the mechanisms underlying this finding require further study [55]. Several lines of evidence, including virtual lesions [56•,57] and other investigative approaches [58], indicate that bilateral supranormal activations arising after stroke – whatever their basis is and despite the fact that they are seen most often in weaker patients – do contribute to whatever behavioral recovery spontaneously arises after stroke. Inflammation has an important relationship with poststroke repair [59], highlighting the importance of reports of microglia traffic measurement during the first month after stroke [60].

One principle emerging across human brain studies is that baseline functional anatomy influences the pattern of poststroke functional anatomy. Thus, swallowing [61], facial movement [18], and gait [62] are normally more

bilaterally organized than distal extremity movements. Also, after stroke, a shift away from the ipsilesional hemisphere in the balance of hemispheric activity occurs most often and with greatest clinical gains in these tasks. This principle suggests the hypothesis that behaviors that are more bilaterally organized in the normal state might benefit from a more bilateral approach to therapy.

Genetic factors probably also have important influences on poststroke repair in humans. Brain-derived neurotrophic factor (BDNF) is among the most abundant growth factors in mammalian brain, being necessary for many neuronal functions. A single nucleotide polymorphism producing a valine to methionine amino acid substitution at codon 66 occurs in one or both human alleles in more than 27% of the American population [63]. Kleim *et al.* [64••] found that individuals with the BDNF val66met polymorphism in one or both alleles exhibited significantly impaired short-term experience-dependent motor cortex plasticity. Given the importance of cortical plasticity to behavioral recovery after stroke, this finding suggests that this polymorphism might have an important influence on behavioral outcome after stroke. Observations such as those of Siironen *et al.* [65], who found that the presence of this polymorphism was associated with a poorer outcome after subarachnoid hemorrhage, support this hypothesis.

Examination of the phases of brain repair during the weeks after a stroke suggests distinct poststroke temporal epochs, each requiring specific therapeutic approaches. Similar models have been described in the motor [66] and language [13] systems.

Promoting repair after stroke

A number of therapies, representing divergent approaches, are in development to enhance behavioral outcome beyond that attained spontaneously. The state of development of these therapies ranges from preclinical investigation to late phase human trials.

A number of small molecules show promise for promoting brain repair after stroke. Some, such as extended-release niacin [67] and sildenafil [35], have prior human applications in other medical indications. Hopes have been high for amphetamine in light of prior small positive reports, but a randomized, double-blind, placebo-controlled trial of 5 weeks of amphetamine in 71 patients with subacute stroke did not demonstrate a drug-related benefit [68•]. Neutralization of the axon growth inhibitor Nogo-A with monoclonal antibodies might be useful in a number of neurologic conditions, including stroke [40].

Growth factors play an important role in development and spontaneous brain remodelling, and so it is not surprising that they are emerging as potentially important restorative agents. Examples of preclinical effectiveness with exogenous growth factors include BDNF [69] and granulocyte-colony stimulating factor [36]. Kolb *et al.* [34] found that sequential administration of epidermal growth factor and erythropoietin reduced deficits, in some cases when treatment was initiated 7 days after stroke onset, with this on the heels of a positive small study showing safety and benefits from erythropoietin delivered within 8 h of stroke onset in humans [70]. The issue of the blood–brain barrier effects on accessing biologic targets might be important, with a solution being use of a 'trojan horse' approach [38].

The use of exogenous cells is receiving increased attention in stroke. A small trial in human patients with subacute stroke found marrow stromal cells to be safe and possibly effective in reducing disability [71]. The time window after stroke during which intravenous marrow stromal cells improve final outcome in rats is now known to be at least 1 month [72••]. Other forms of exogenous stem cells have shown promise in related neurologic conditions [73,74]. Genetic modification of marrow stromal cells permits local delivery of specific growth factors, with behavioral gains [37,75–77]. Inducing changes in the number and behavior of endogenous stem cells might also be an important approach [78].

The brain is an electrical organ, and not surprisingly electromagnetic stimulation can modulate a number of functions and behaviors. Repetitive TMS can have inhibitory or excitatory effects on cortical activity [79]. As such, goals can include increasing activity in ipsilesional cortical regions that are underactive [80,81], or in contralesional cortical regions that are overactive and a source of potentially harmful inhibition [82]. Transcranial direct current stimulation has also shown promise in initial studies [83]. Epidural motor cortex stimulation can also improve motor function after stroke [83]. In these approaches, brain mapping studies might be useful to direct the site of stimulation [84].

A number of devices that interface directly and indirectly with the human central nervous system are in development to improve function after stroke. Examples include a direct brain–computer interface to modulate motor function [85•] or alertness [86]. Methods for less invasive acquisition of brain output to drive such devices are under exploration [87]. Robotic devices continue to be developed to improve functional status after stroke [88]. Robotic therapies offer potential advantages in that they can be active without fatigue for very long time periods, they can perform in a consistent and precise manner, they can be programmed, they have the capacity to measure

a range of behaviors, and they are enabled for telerehabilitation [89,90]. Functional electrical stimulation can also improve outcome after stroke [91].

Physiotherapy interventions will probably be an important component of many restorative therapies, alone or as an adjunct. The EXCITE (Extremity Constraint Induced Therapy Evaluation) trial, a single-blind, customary care-controlled, randomized, multisite trial of 222 patients with moderate motor deficits from a first stroke 3–9 months previously, demonstrated effectiveness of constraint-induced movement therapy (CIMT) [92••]. Although evidence suggests that increased time in therapy early after stroke can improve functional outcome [93], application of CIMT very early after stroke at high intensity can be deleterious [94]. Modified forms of CIMT might increase the fraction of patients who benefit from this intervention [95]. A number of other forms of therapy are also under evaluation, including motor imagery, observation, and imitation, including use of virtual reality approaches [96–101].

Optimizing approaches to repairing the brain after stroke in humans

Maximal gains from these restorative therapies might be achieved if they are applied in light of insights into the neurobiology of poststroke repair presented above. Thus, measurement of features of central nervous system function might serve as guides to some features of restorative therapies after stroke. There are numerous examples in the practice of medicine whereby the physiologic state of the target tissue is probed to guide decision making and thereby maximally reduce symptoms. Examples include use of pulmonary function tests to guide treatment of chronic obstructive pulmonary disease, measurement of serum thyroid-stimulating hormone to guide treatment of hypothyroidism, and use of exercise treadmill testing to guide treatment of coronary artery disease.

Approaches to applying functional neuroimaging in this context are at a relatively early stage. One domain of application is as a biologic marker of treatment effect, providing secondary measures of treatment effect as well as insights into treatment mechanism. One recent meta-analysis [102] examined studies that have employed functional neuroimaging as a biologic marker of treatment effects targeting stroke. Conclusions across 13 studies included that motor deficits have been most often studied, that published studies have focused on patients with good to excellent outcome at baseline, and that there is a paucity of functional neuroimaging conducted to examine treatment effects during the first few months after stroke. The review also concluded that further study is required into the effects of key variables such as lesion site, concomitant diagnoses (e.g. depression), sex, and age on the performance of functional neuroimaging in this context.

Another domain of application is to predict treatment response; such data might be useful in patient selection. A number of initial efforts in this direction have been reported, in small cohorts. Stinear *et al.* [103] examined 17 patients with chronic stroke. Baseline measures that predicted motor gains across 30 days of motor practice therapy included fractional anisotropy, a diffusion tensor-based measure of white matter integrity, in the posterior limb of internal capsule. Results varied according to physiologic properties of the corticospinal system. Cramer *et al.* [104•] examined 24 patients with chronic stroke before and after 6 weeks of rehabilitation therapy with or without investigational motor cortex stimulation. Several baseline measures correlated with subsequent trial-related clinical gains and were entered into a forward stepwise multiple linear regression model, which found that two baseline measures had independent value for predicting clinical gains: baseline arm motor status and an fMRI-based measure of motor cortex function (with lower motor cortex activation predicting greater potential to improve with therapy). Interestingly, greater treatment-related gains were associated with greater increases in motor cortex activation over time. Koski *et al.* [105] found that change in TMS measures across the first two therapy sessions predicted response to subsequent weeks of motor therapy. Dong *et al.* [106] found that the fMRI laterality index midway through motor therapy predicted subsequent behavioral gains. The latter two studies suggest that functional neuroimaging might also be able to aid in selection of restorative therapy dose.

A number of other avenues are under study to improve the approaches used to administer restorative therapies after stroke. Establishment of standardized protocols for functional neuroimaging might reduce several sources of variance [107,108]. Disentangling behavioral compensation from actual recovery might be of high importance [109]. Assessment of a range of neurologic domains might maximize the likelihood of detecting changes in a subset of neurologic domains, an approach that is more difficult when relying exclusively on global neurologic scales to measure therapeutic effects.

Conclusion

Studies in animals have provided insights into the neurobiology of spontaneous behavioral recovery after stroke, and in doing so they have helped to define a number of therapeutic targets to improve outcome further. Brain mapping studies have provided insights into this repair in humans, with results showing many points of overlap with animal studies. Furthermore, brain mapping can be a useful source of information relevant to

decision making in the setting of a restorative intervention trial in humans with stroke.

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