

Imaging Motor Recovery After Stroke

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Summary: Most patients show improvement in the weeks or months after a stroke. Recovery is incomplete, however, leaving most with significant impairment and disability. Because the brain does not grow back to an appreciable extent, this recovery occurs on the basis of change in function of surviving tissues. Brain mapping studies have characterized a number of

processes and principles relevant to recovery from stroke in humans. The findings have potential application to improving therapeutics that aim to restore function after stroke. **Key Words:** Stroke, plasticity, human brain mapping, recovery, therapy, functional MRI.

INTRODUCTION

Stroke is the third leading cause of death and the leading source of adult disability in the United States. A number of neurological domains can be impaired after stroke, the most common of which is the motor system.^{1,2} In most patients, the time when spontaneous return of motor function is seen spans from 1 to 3 months after a stroke.^{3,4} For most patients, however, this recovery is incomplete and significant impairment and disability remain.

The severity of residual poststroke motor deficits varies widely. A number of factors have been examined as predictors. For example, severity of initial neurologic injury has been shown as best predictive factor of outcome, with patients having mild to moderate initial stroke deficits showing an excellent prognosis but patients having severe baseline stroke deficits showing a more variable recovery.⁵ In one study, a relative improvement of the initial motor score of about 20% in the first 4 weeks after stroke was associated with good outcome.⁶

Indeed, many measures have been found to predict spontaneous poststroke recovery. Age, cognitive impairment, sensory or motor evoked potentials, early measures of brain function, accompanying neurological deficits, volume of injury, magnetic resonance imaging

(MRI) spectroscopic nature of injury, and location of injury have each been found to have value for predicting recovery and final motor status after stroke.^{6–19} Such a long list is not surprising, however, given the large number of factors known to influence brain function after stroke (Table 1).²⁰

The mechanisms by which spontaneous recovery occurs in humans have undergone considerable study in recent years. Available evidence in humans^{21–28} and animals^{29–35} suggests that surviving elements in the adult mammalian brain reorganize function as a major contribution to spontaneous behavioral recovery. Multiple methods have been used to study these changes in brain function that arise after a stroke. Each method has its relative strength and limitations.

The current review is focused on functional magnetic resonance imaging (fMRI), with an emphasis on recovery of motor function, which is among the major sources of impairment in stroke patients. The overall goal of these studies is to better understand reorganization of brain function, with one long-term goal being to suggest new approaches for improving patient outcomes. Such a goal might be realized by better prediction of outcomes, improved patient triage, defining (perhaps at the level of the individual patient) features of restorative therapy dose, and suggesting new treatment approaches.

A number of study designs have been used to employ human brain mapping in the evaluation of recovery after a stroke in humans. Longitudinal and cross-sectional imaging approaches are two fundamental strategies.²⁷ Initial functional imaging studies were small, cross-sectional

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Table 1. *Clinical Variables That Likely Modify Brain Function After Stroke*

Stroke topography and sites injured
Time poststroke
Age
Hemispheric dominance
Side of brain affected
Depression and psychiatric comorbidities
Injury to other brain network nodes
Infarct volume
Initial stroke deficits
Arterial patency
Medical comorbidities
Prestroke disability, social function, experience, and education
Type and amount of poststroke therapy
Acute stroke interventions
Medications during stroke recovery period
Final clinical status
Stroke mechanism
Genetics

tional, and observational in nature. These studies investigating patients at a single time point after motor system injury reveal patterns of lesion-induced reorganization both in acute and chronic stroke patients. On the other hand, longitudinal studies provide insights into course of changes in cerebral motor activation and functional improvements over time and how this reorganization evolves in relation to behavioral recovery. Behavioral probes employed during brain mapping have varied, too, being monotonic or parametric, singular or multiple, and evaluated via a single modality or via a multimodal approach.

RECOVERY OF MOTOR FUNCTIONS AND IMAGING

Ample data from studies in animals and humans have shown that the brain has the capacity to change structure and function, in association with behavioral recovery, in the days and weeks after a stroke. Studies in animals undergoing an experimental unilateral infarct have characterized the molecular and cellular substrates of this plasticity that is present in perilesional and distant brain regions.^{22,29–31,36,37} Furthermore, exogenous interventions such as amphetamine,³⁴ growth factors,^{38,39} cellular therapies,^{40,41} brain stimulation,^{33,42} increased environmental complexity,^{43,44} and physical activity level⁴⁴ can amplify these molecular events in parallel with improvements in behavioral outcome.

There is little doubt that translation of results of animal studies into human studies is of great value in understanding the biology of recovery after stroke. However, there are several limitations to this approach.⁴⁵ One issue is that quadruped rodents, the subjects of most animal studies, have a different brain organization from

humans, including relative size of basal ganglia and white matter. Second, animal models often lack the heterogeneity of injury found in human condition, or at times the relevance to human forms of ischemic injury. Also, animal models can have a more uniform preinfarction behavioral status (generally, they are at a younger point in life span) and most human stroke risk factors are not present in animal models.

Therefore, the study of humans is of critical value to improving understanding and therapeutics for stroke recovery in humans. Human brain mapping with fMRI and other techniques provides insights into the brain events underlying the spontaneous return of function after stroke. A long-term goal of brain mapping studies of stroke recovery is to generate an improved understanding of restorative neurobiology. Application of this knowledge could lead to improved therapeutics and reduced poststroke disability.

Changes in the area surrounding an infarct are likely important to spontaneous behavioral recovery after stroke.^{36,46,47} Animal studies have described a wide range of molecular, cellular, and cortical map changes in the area surrounding an infarct. Such changes occur at a greater than normal level, persist chronically, and in many cases have been interpreted as important to poststroke behavioral recovery.^{34,36,48–54} Furthermore, in some cases these events can be further amplified by therapeutic intervention, a phenomenon that has been associated with additional behavioral gains.^{33,34,40,42}

In humans, studies have found that the volume of threatened but surviving peri-infarct tissue is directly related to final clinical outcome.^{55,56} A number of functional neuroimaging studies, using a range of imaging modalities, has specifically noted activation in the peri-infarct region of patients with chronic stroke (e.g., Refs. 47 and 57–63). A recent fMRI study did not find that extent of peri-infarct activation correlated with outcome after stroke.⁶³ However, the T2*-weighted MRI signal used to measure brain activation with fMRI is itself altered in the peri-infarct zone. The results suggest that further studies are needed to understand the relationship between increased tissue T2* signal and fMRI activation. Also, brain mapping methods besides fMRI^{64–67} might be needed to best study this potential recovery mechanism.

Changes in areas distant from injury likely make a major contribution to spontaneous recovery after stroke. One example of this is resolution of diaschisis. Diaschisis refers to reduced blood flow and metabolism in uninjured brain areas that have rich connections with injured brain areas.^{17,68,69} Studies have shown that behavioral recovery is related to resolution of diaschisis; i.e., restitution of brain activity in uninjured areas that are distant from, but connected to, the site of infarct.^{70–72}

Another form of change in areas distant from injury is

the multifocal increase in activation seen across large networks after stroke. Since the first functional imaging study of brain function after stroke,⁷³ human brain mapping studies have emphasized increased activation after stroke within multiple nodes that together comprise distributed networks.^{57,59,74–84} Maintenance of behavioral output after injury to a network is, in general, associated with increased network activation.

The focus of initial brain mapping studies was on subjects with very good behavioral outcome. However, studies enrolling patients with a broader range of outcomes have emphasized that, within many secondary cortical regions, lesser outcome is often associated with a greater degree of activation, possibly reflecting increased effort or demand.^{85,86} The nature of the relationship between outcome and activation extent might be different in primary neocortex, however, as described below.

The association between increased activation post-stroke and lesser outcome extends to recruitment of contralesional networks. Studies suggest that shift of activation balance toward the contralesional hemisphere is common in the early days and weeks after a stroke. Subsequently, patients in whom the balance returns toward the stroke-affected hemisphere in the chronic phase have better behavioral outcomes, while patients in whom the balance remains tilted toward the contralesional hemisphere chronically have poorer behavioral outcomes.^{82,85–90} This finding might in part relate to changes in the balance of interhemispheric inhibition.^{91–95} However, in the patients with poorer outcomes, this supranormal contralesional recruitment likely does contribute to the small but real behavioral recovery that does occur.^{96–98}

Results are less clear regarding the effect that injury to a primary cortical area, or its efferents, has on activation within that area. In the motor system, functional neuroimaging studies have reported that better motor outcome can be associated with larger activation within the primary motor cortex, smaller activation, a mosaic of the two, or no effects.^{57,85,99–103} These differences across studies might relate to different features of the studied populations, such as injury topography or time poststroke, or to the use of different functional neuroimaging endpoints. Results are clearer when motor system function is probed using neurophysiological methods such as transcranial magnetic stimulation (TMS), where better motor outcome has been associated with a larger degree of integrity within the injured corticospinal tract. Functional neuroimaging studies in the language system also converge on this latter finding, showing that better language outcome is associated with larger activation within the left hemisphere primary language cortex.

THERAPEUTIC INTERVENTION AND RECOVERY

A number of restorative interventions are under study, including cells, selective serotonin re-uptake inhibitors, catecholaminergics, regional electrical stimulation of brain, genetic manipulations, neuroprostheses, robotics, imagery-based protocols, and function-oriented physical therapy regimens.^{34,35,39,40,104–109} However, none is a currently approved therapy for enhancing outcome after CNS injury such as stroke. The maximum value of functional neuroimaging methods such as fMRI will be appreciated when used to improve application of an established restorative intervention.

Measures of brain function are useful for understanding how iatrogenic interventions improve behavioral outcome.^{110–120} Brain mapping data are also useful for predicting outcome, and therefore perhaps for triaging.^{71,121–125} In addition, fMRI can be used to guide features of therapeutic intervention after stroke.¹²⁰ Two potential examples for brain mapping interacting with application of a poststroke therapy follow.

One emerging therapy is constraint-induced motor therapy, which has been shown as effective to overcome a learned reduction in use of a weakened extremity. Though motor gains through an intervention that improves chronic weakness are not the same as spontaneous recovery, many of the same principles might apply. Several studies have shown changes in cortical function with associated motor recovery, including the use of electroencephalogram, fMRI, and TMS.^{114,117,126–129} This type of intervention has been shown to be efficacious in chronic,^{130,131} subacute,¹³² as well as acute¹³³ stroke patients, with motor improvements that are long lasting.¹³¹ Changes in brain function after constraint-induced motor therapy include altered motor excitability, a shift in recruited brain areas, a change in motor system laterality, and an increase in affected hand motor representation area.¹³⁴ These divergent changes in brain function likely reflect differences in patients (therapy might have different effects on laterality of brain function in more severely affected patients¹¹⁴ than on less severely affected¹¹⁷), therapy duration, and study methods. As with spontaneous stroke recovery, further functional neuroimaging studies might have the potential to clarify treatment mechanism, optimize details of therapy, and improve patient selection.

Another of the therapies under evaluation to improve motor function after stroke is the boost in motor function seen with modulation of somatosensory feedback from the affected limb. Somatosensory stimulation of the median nerve of the affected hand of chronic stroke patients has been reported to increase muscle strength.¹³⁵ Conversely, reducing somatosensory input from the unaf-

affected hand with a regional anesthesia during hand motor practice, induced improvement in motor function of paretic hand including some activities of daily living.¹³⁶ Similar results have been observed with intensive neuromuscular stimulation of the affected hand, with an increase in cortical activation in the ipsilateral somatosensory cortex.¹¹¹ The sensorimotor integration theory might provide insight into the basis for these motor gains; motor output is inextricably linked to sensory input and movements cannot be properly produced without appropriate sensory input patterns.^{137,138} This theory provides a rationale for active assistive therapy.¹³⁹ Integration of the sensorimotor integration theory might be improved with the measurement of function in brain areas key for such integration.^{140,141}

Interventions that change brain function and produce enduring behavioral gains have been described in patients with subacute stroke and with chronic stroke. The time elapsed since stroke onset does not appear to be a limiting factor for this effect. Regardless of the form of therapy under evaluation, measuring the function of the target organ is likely useful for defining features of therapy. Thus, for the brain recovering from stroke, some measure of brain function will likely be found useful for therapy selection, dosing, or duration.^{58,60–62}

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