MRI of Stroke Recovery

Quan Jiang, PhD, **Zheng Gang Zhang, MD, PhD**, and **Michael Chopp, PhD**
Department of Neurology, Henry Ford Health System, Detroit, Mich.

Abstract

MRI is a vital tool for the measurement of acute stroke and has been used to visualize changes in activation patterns during stroke recovery. There is emerging interest on using MRI to monitor the structural substrates of spontaneous recovery and neurorestorative treatment of stroke. In this review, we describe the use of MRI and its associated challenges to measure vascular and neuronal remodeling in response to spontaneous and therapy-induced stroke recovery. We demonstrate that MRI methodologies may be used in real-time monitoring of recovery from stroke.

Keywords

MRI plays a major role in the management of the patient acutely after stroke.[1] MRI has been primarily focused on the acute management of stroke, staging of ischemic damaged tissue, especially identification of reversibly damaged ischemic tissue, with the goals of extending the treatment window, and early detection and prediction of ischemic damage.[1] However, only a small percentage of patients with stroke can be accessed and treated within the thrombolytic treatment window of 4.5 hours. It is important to have alternate treatment strategies, particularly restorative therapies, with a less restrictive therapeutic window that can be applied to a large population of patients with stroke and concomitantly to develop advanced neuroimaging methodologies to monitor stroke recovery.

Experimental studies suggest that cell-based or pharmacological-based neurorestorative treatments can enhance brain reorganization and substantially improve functional recovery when treatment is initiated up to weeks after stroke.[2] Neurorestorative treatments amplify endogenous processes of brain plasticity, including angiogenesis and neuronal remodeling through neurogenesis and axonal reorganization, which likely contribute to improvement in neurological function after stroke.[2] Current understanding of angiogenesis, neuronal remodeling after stroke, however, derives mainly from regional histological measurements, which do not allow dynamic assessment of tissue remodeling.[2] In contrast, MRI can noninvasively monitor the temporal profiles of functional recovery and tissue remodeling after stroke.[3-5]

The traditional MRI method for monitoring stroke recovery is functional MRI (fMRI).[5] Increased recruitment of functional activity in the contralateral hemisphere after stroke indicates poor recovery.[5] Renormalization of activity reflects a better recovery in which the

Correspondence to Quan Jiang, PhD, Henry Ford Hospital, NMR Laboratory, Neurology Department, 2799 West Grand Boulevard, Detroit, MI 48202. qjiang1@hfhs.org.

initial overactivation in the contralateral hemisphere decreases and the functional activation of the primary cortex in the ipsilateral hemisphere recovers over time.[5] Direction of local remapping from the primary cortex may also affect recovery after stroke, that is, better behavioral outcome is associated with a more posterior and worse outcome with more anterior motor activation. fMRI has also been applied to investigate the effects of rehabilitation on stroke recovery. Improved grip strength after constraint-based therapy corresponds to an increased activation in the ipsilateral premotor, secondary somatosensory, and bilateral superior posterior cerebellum areas in patients with stroke.[5] Exercise-mediated improvements in walking velocity correlate with increased activation in the cerebellum and midbrain in patients with stroke,[6] and lower activation in the stroke-affected motor cortex at baseline predicts behavioral gains after rehabilitation therapy. The ability of fMRI to predict functional recovery was also suggested in a stroke trial with arm-forced therapy.[7]

Recent developments of fMRI have focused on brain network changes during stroke recovery.[5,8] Brain function depends on a distributed network connected in complex and overlapping circuits. Thereby, functional recovery after stroke shows changes not only in localized activity in the specific region in response to a distinct functional task, but also in the integrated activation over the network. Advanced fMRI methods have been developed to investigate the interactions between brain regions[8] and to investigate changes in brain connectivity after stroke.[5,8] Patients with stroke, compared with healthy control subjects, exhibited decreased intrinsic neural coupling between the primary motor cortex and cerebellum corresponding to dysfunctional motor cortex and cerebellum connection, increased coupling from the supplementary motor area to the primary motor cortex, and from the supplementary motor area to the cerebellum, suggesting that changes in the supplementary motor area and cerebellum connectivity may occur to compensate for a dysfunctional primary motor cortex.[8]

Functional MRI and fMRI connectivity information is based on hemodynamic changes in blood oxygen extraction rate, cerebral blood flow, and cerebral blood volume (CBV).[5] Although fMRI provides crucial information related to stroke recovery, fMRI does not provide data related to changes in brain structure after stroke. Neurological outcome after stroke is correlated with vascular and neuronal remodeling, which can be monitored by MRI in preclinical models of stroke.[3,4,9] Due to the noninvasive nature of MRI measurement, the MRI indices of vascular and neuronal remodeling related to neurological outcome in preclinical stroke study may be translated to the clinic. Therefore, in this review, we focus on select MRI methodologies that visualize dynamic brain tissue reorganization after stroke with particular attention given to vascular and axonal reorganization after stroke.

MRI Measurements of Vascular Reorganization After Stroke

Vascular remodeling likely contributes to neurological recovery poststroke.[2] Higher cerebral blood vessel density predicts improved outcome and survival in patients with stroke.[10] Neurorestorative treatments after stroke induce angiogenesis.[2] Treatment of stroke in rats with neurorestorative therapy increases levels of vascular endothelial growth factor (VEGF), which consequently enhances angiogenesis and arteriogenesis primarily in the boundary zone of the ischemic lesion and reduces functional deficits.[2] VEGF promotes vascular remodeling and induces angiogenesis and arteriogenesis.[11] These newly formed vessels are important for tissue perfusion, but most likely their benefit derives from the factors expressed by newly formed vessels such as brain-derived neurotrophic factor, VEGF, VEGFR2 and matrix metalloproteinases such as matrix metalloproteinase-2 and matrix metalloproteinase-9.[11]

Newly formed cerebral vessels are inherently leaky, because it can take several weeks to form a functional blood–brain barrier.[4] An early approach in detecting angiogenesis by MRI was to monitor changes in blood volume with time, which may reflect the growth of new blood vessels.

[12] A significant correlation was found between dynamic contrast-enhanced MRI blood volume measurements and histological determination of microvessel density in angiogenic hot spots. [12] Elevated CBV correlates with increased vascular density in patients with gliomas.[12] However, an inherent flaw in the correlation of CBV with vascular remodeling may arise from increased vessel diameter, resulting in an increased blood volume fraction that does not necessarily reflect increased number of vessels as determined by mean vascular density (MVD).[12]

VEGF increases vascular permeability in addition to angiogenesis.[4,9] On activation of VEGF receptors by VEGF, microvessels become hyperpermeable to plasma proteins and other circulating macromolecules. Such hyperpermeability accompanies angiogenesis in tumors, healing wounds, retinopathies, inflammatory conditions, and physiological ovarian angiogenesis.[12] Quantitative evaluation of the leakage of contrast across the blood– brain barrier has been implemented as dynamic contrast-enhanced MRI using classical tracer kinetic theory.[13] Dynamic contrast-enhanced MRI permits measurement of permeability, most frequently, the blood-to-brain transfer constant (K_i) of Gd-DTPA. The initial K_i, obtained using a deconvolution method, was highly model-dependent.[13] The Patlak model and plots with simplified model assumptions have been successfully applied to analyze dynamic contrast-enhanced MRI data and to evaluate K_i[14]. These data and the Patlak plot approach for analyzing MRI findings were confirmed with the images and K_i results obtained with ^{14}C-sucrose quantitative autoradiographic in the same animals.[14] K_i has been applied to reproducibly measure vascular permeability in patients with cancer. MRI CBV, cerebral blood flow, and K_i have also been used to measure angiogenesis after stroke.[4,9] MRI images of neural progenitor cell therapy of stroke in the rat show enhanced angiogenesis in the ischemic boundary regions after cell-based treatment, confirmed by an increase in vascular density and the appearance of large thin wall mother vessels in 3-dimensional laser scanning confocal microscopy.[4] The enhanced angiogenesis colocalized with increases of cerebral blood flow and CBV at 6 weeks after treatment and colocalized with transient increases of blood-to-brain transfer constant (K_i) of Gd-DTPA with a peak at 2 to 3 weeks after cell therapy.[4] These MR measurements, along with advanced analysis using iterative self-organizing data, identify the location and area of vascular remodeling and angiogenesis.[4] K_i is a sensitive parameter to detect the early stage of angiogenesis during stroke recovery based on similar mechanisms of angiogenesis in tumor. However, tumor exhibits a constant increase in K_i due to the continuous growth of new vessels, whereas a transient increase in K_i, with a short time window, is demonstrated after restorative treatment of stroke.[4] Therefore, the sensitivity to detect angiogenesis using K_i is time-dependent during stroke recovery.

In addition to cerebral blood flow, CBV, and K_i MRI measurements of angiogenesis after stroke, susceptibility-weighted imaging (SWI) incorporating phase information is highly sensitive to angiogenesis.[9] The phase information that is generally discarded is strongly dependent on local variations in susceptibility. The susceptibilities of fully deoxygenated and fully oxygenated blood differ by 0.18 ppm with oxygenated blood being slightly diamagnetic ($\Delta\chi=-0.026$ ppm) and deoxygenated blood paramagnetic ($\Delta\chi=0.157$ ppm). Thus, small changes in the concentration of deoxyhe-moglobin will be sensitively reflected in the phase of the local magnetization vector as it evolves in the MRI experiment. This sensitivity is used in SWI to form images of very small venous vascular features.[15] Because angiogenesis typically occurs in regions of high oxygen extraction, SWI provides early images of small draining veins in peri-infarct regions that are likely to promote angiogenesis. A combination of SWI and K_i may also provide information about the stage of angiogenesis.[9] K_i transiently increases during the early stage of vessel formation, whereas draining veins appear in SWI after the veins become functional. These MRI measurements could offer an indirect means of detecting newly formed vessels. SWI is currently being tested in a number of centers and is an emerging technique to improve the clinical diagnosis of neurological trauma, brain neoplasms, and

neurovascular diseases because of its ability to reveal vascular abnormalities and microbleeds.[15]

Angiogenesis evokes an increase in MVD. Several authors have used MRI to estimate vessel size, and this can be correlated with blood volume as a means of inferring MVD.[16] The ratio of changes in gradient-echo to spin-echo relaxation rate ($\Delta R_2^*/\Delta R_2$) induced by a high-molecular-weight intravascular contrast agent may provide an indication of average vessel size in a voxel under certain conditions related to echo time, contrast concentration, and the main magnetic field.[16] $\Delta R_2^*/\Delta R_2$ is a dimensionless ratio, and its expression in terms of tissue model parameters depends not only on vessel size distribution, but also contrast concentration and the water diffusion coefficient.[16] To avoid strong dependency on contrast concentration, the new quantity $Q \equiv \Delta R_2/(\Delta R_2^*)^{2/3}$ that involves only intrinsic properties of the vascular network has been suggested. Q is sensitive to vessel density but not size.[16] MRI measurement of MVD, primarily performed in conjunction with tumor, has been recently applied to angiogenesis during stroke recovery.[17] By direct comparison of MVD measured between MRI and corresponding immunostained sections, a good agreement in the intracorrelation coefficient (0.85; *P*<0.05) and high correlation (*r*=0.90) was observed in the recovery region and normal contralateral hemisphere. However, large errors in MRI MVD were encountered in the ischemic core.[17] MRI MVD measurements exhibit promise for quantitative evaluation of microvascular changes in the brain tissue after stroke.

The vascular changes caused either by new vessels or altered vascular architecture provide MRI detectable signatures, which can be used to monitor these vascular events and to relate these events to neurological recovery poststroke. Although these vascular MRI measurements are currently used in preclinical stroke studies, all of them can be readily translated to the clinic.

MRI Measurements of Axonal Remodeling After Stroke

Neurorestorative therapy also enhances neuronal remodeling, for example, promoting axonal growth and remyelination, new axonal sprouting, synaptogenesis, and endogenous neurogenesis, all of which contribute to functional recovery.[11] Stroke evokes molecular and cellular changes in the ischemic boundary and in remote ischemic brain areas, proliferation of neural stem and progenitor cells, differentiation of neural progenitor cells, migration of neuroblasts to ischemic boundary, and unmasking of previously inhibited connections.[11,18] Inhibition of axonal sprouting predominates in the healthy brain, which is controlled by myelin-associated proteins, extracellular matrix proteins, and growth cone inhibitors. Ischemic injury induces axonal sprouting.[11,18] Neurorestorative treatment of stroke significantly increases both progenitor and mature oligodendrocytes in the ipsilateral hemisphere of the ischemic brain. [18] Oligodendrocytes generate myelin and contribute to the integrity of white matter tracks in the brain. Stimulation and amplification of these cells may lead to restructuring of axons and myelin. White matter architecture in the ischemic boundary is altered by neurorestorative treatment, and axonal density in the peri-infarct area is significantly increased in the treated animals.[3,18] Pseudorabies virus labeled with green fluorescent protein and red fluorescent protein has been used to demonstrate axonal remodeling in an experimental stroke animal model with spontaneous recovery and after restorative cell therapy.[19]

MRI has the unprecedented ability to obtain structural and physiological information on the brain. Diffusion tensor MRI (DTI) based on the movement of water provides a means for delineating the anatomic connectivity of white matter pathways and can be used to detect pathological tract disruption. DTI provides 2 scalars called apparent diffusion coefficient and fractional anisotropy (FA), which characterize the magnitude of water diffusion and the degree of anisotropy, respectively, for each voxel. In addition, axial (parallel to the long axis of fiber) and radial (perpendicular) diffusivity are given by corresponding eigenvector values, which

may be related to axonal (axial diffusivity) or myelination (radial diffusivity) status. FA reflects histological markers of myelination. Increased FA correlates with white matter tract integrity, whereas reduced FA is correlated with functional deficits.[20] Loss of anisotropy has been reported in normal aging in both acute (stroke, transient ischemic attack) and chronic (amyotrophic lateral sclerosis, multiple sclerosis, small vessel disease) neurological diseases and schizophrenia. Reduction of FA in patients with Wallerian degeneration after ischemic stroke is negatively correlated with functional recovery.[21] The degree of FA reduction may be predictive of functional outcome in patients with stroke.[20] Corticospinal track integrity is also associated with stroke recovery.[19]

Previous investigations have primarily focused on the relationships of white matter damage measured by DTI and stroke recovery[20] with less attention paid to the effects of white matter reorganization on stroke recovery. Recent studies have shown that restorative treatment of stroke promotes axonal remodeling and increases oligodendrocytes (remyelination).[11] FA may be able to identify ischemia-injured cerebral tissue undergoing white matter reorganization after restorative treatment. Axonal projections emanating from individual parenchymal neurons exhibit an overall orientation parallel to the lesion areas after stroke.[3] White matter reorganization, confirmed by an increase in axons and myelination, after neural progenitor cell treatments is coincident with increases of FA in the ischemic recovery regions.[3] Also, the fiber tracking maps derived from DTI reveal that axonal projections emanating from individual parenchymal neurons exhibit an overall orientation parallel to lesion areas after stroke, similar to the orientation patterns formed in immuno-histological measurements. White matter reorganization was also detected in patients by using DTI measurements at multiple time points after intracerebral hemorrhage. Jang et al[22] show FA and apparent diffusion coefficient renormalization in the corticospinal track 5 months after intracerebral hemorrhage corresponding to significant motor functional recovery. The affected regions of the right corona radiata and the internal capsule have lower FA and higher apparent diffusion coefficient in patients with complete paralysis of the left extremities 3 weeks after intracerebral hemorrhage. An interrupted corticospinal track was also observed at the right middle corona radiata on the 3-week diffusion tensor tractography, whereas no such corticospinal track interruption was detected on the 5-month diffusion tensor tractography.

The recent neuronal reorganization results challenge a basic MRI concept in the field of stroke therapy, that is, that an increase in T2 identifies irreversible ischemic damage of brain tissue. Ischemic tissue with a large T2 increase acutely after stroke did not die, and the ischemic tissue located in the core lesion areas contiguous with and extending into the corpus callosum survived at the chronic phase after stroke with cell-based treatment.[3] This observation of the recovery of ischemic tissue with a large T2 increase suggests that a much longer treatment window may be available in patients with stroke than previously thought.

To date, conventional DTI remains dominant in the investigation of white matter damage and reorganization. However, when white matter fiber tracts cross, conventional DTI produces an anomalous result, showing an overall lowering of FA despite the presence of highly oriented tissue. The inability of conventional DTI to resolve multiple fiber directions derives from the assumption of Gaussian diffusion inherent to the diffusion tensor model.[23] The conventional tensor model assumes Gaussian diffusion, and a Gaussian function has only a single directional maximum. Consequently, the conventional tensor model cannot capture multidirectional diffusion. In brain regions containing fiber-crossing, the MR diffusion signal has significant multimodal structure, in clear disagreement with the conventional tensor model.[23] The distribution of the path of water molecules for the time of the MRI experiment can be generated through q-space DTI (q-DTI).[23] There are 2 types of information present in q-DTI, directionality and distance—the mean free path (from the second moment of the probability distribution function of path lengths). Characterization of white matter tracts using q-DTI can

provide mechanistic information between white matter remodeling and functional recovery after stroke. A new q-space anisotropy map based on calculating the SD of diffusion, termed the SD map,[24] has been developed. A high SD value is present in the corresponding high axonal density areas in white matter regions with crossing fibers, where FA failed to detect this white matter reorganization. White matter reorganization early after stroke may involve crossing fibers, which are insensitive to traditional FA measurement. SD may provide information about the stage of white matter rewiring in the injured brain with increased SD alone (without FA elevation) representing an early recovery stage of fiber-crossing, whereas the increased FA identifies more mature linear fibers. This SD method can also be applied to investigate white matter recovery in patients with stroke.[24] Compared with FA, the SD map shows significant white matter reorganization in the ischemic regions with crossing fibers. SD was superior in identifying white matter reorganization during the early stage of stroke recovery. This MRI measurement could provide valuable information to stage white matter remodeling.

Structural changes of white matter in the brain and the cortical spinal track after stroke may underlie and contribute to functional recovery.[20] Changes in axonal density and orientation are diffusion-sensitive and therefore MRI-visible. Induction of stroke increases neurite extension from the intact to the denervated cord.[19] This axonal rewiring is significantly enhanced by neurorestorative treatment. Functional recovery is highly and significantly correlated with the extent of neurite extension from the intact to the affected spinal cord.[19] The relationship of dendritic changes and arborization and MRI has not been investigated, and an MRI index of neuronal architecture would be clinically relevant.

In summary, we have reviewed MRI methodologies to be used to monitor mechanisms related to stroke recovery. Spontaneous recovery is present after stroke, and neurorestorative therapy can enhance the endogenous restorative mechanisms of the injured brain and amplify angiogenesis and axonal remodeling. MRI methodologies can be used to dynamically measure spatiotemporal events related to brain remodeling. Because the noninvasive nature of MRI permits translation of MRI methods from animals to patients, validation of MRI techniques for studying therapy-induced stroke recovery could lead to optimization of neurorestorative treatment protocols and improved management of stroke.

Acknowledgments

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