

Neuroimaging of Stroke and Recovery Using Translational MRI

Abstract

Multiparametric Magnetic Resonance Imaging (MRI) has emerged as an essential clinical tool for assessing the severity of focal ischemic stroke, determining treatment goals and forecasting outcomes. While tissue viability in the vicinity of the stroke is the focus of imaging during the acute phase, the evaluation of distributed structural and functional connectivity is the focus of imaging during recovery. Preclinical MRI of experimental stroke models provides a translational platform for the evaluation of potential therapies and validates noninvasive biomarkers in terms of cellular and molecular mechanisms. The transition from acute to chronic imaging, the fundamentals of common MRI techniques used in stroke research, and experimental results obtained by clinical and preclinical imaging to determine tissue viability, vascular remodeling, structural connectivity of major white matter tracts, and functional connectivity using task based and resting state fMRI during the stroke recovery process are all discussed in this brief overview of translational stroke imaging.

Keywords: Magnetic resonance imaging • Experimental stroke • Biomarkers • Vascular remodeling • Translational stroke imaging • Ischemic stroke

Introduction

Ischemic stroke is the leading cause of complex chronic disability and the third leading cause of death worldwide. As a result of demographic and health care trends that have resulted in rising rates of cardiovascular disease but decreasing rates of stroke mortality, an ever increasing number of people are enduring the effects of ischemic stroke. Some kind of long term assistance is required by up to 75% of stroke survivors. Only recanalization therapy to restore perfusion is available to treat stroke acutely, and only about 2% of patients receive this intervention, despite the urgent need for better therapies at all stages from stroke onset to recovery [1,2].

Literature Review

Numerous pharmacotherapies and novel strategies have been shown to be effective in animal studies in the weeks and months following a stroke. In fact, numerous drugs have shown promise for improving certain aspects of recovery in small clinical trials. The astonishing heterogeneity surrounding neuroplasticity and regeneration” is one of the

obstacles to addressing stroke treatment and determining recovery efficacy. Neuroimaging has largely revealed this heterogeneity in the clinical setting. By providing functional and anatomical markers of the condition of the tissue, imaging aids in the diagnosis, treatment, and recovery of ischemic stroke. Imaging can reduce biological variance within groups by narrowing inclusion criteria based on the initial insult for the purpose of studying recovery processes and therapies. Through longitudinal studies, non-invasive neuroimaging studies can help define the natural evolution of neurodegeneration and plasticity as well as the benefits of therapies. The translational nature of imaging can help clarify differences in underlying processes between species and differences in responses to therapies, both of which frequently fail in the clinic [3].

Discussion

Acute stroke

Some recovery of tissue function can occur for severe ischemia up to an hour given prompt and complete reperfusion, despite the widespread consensus that complete recovery

Alex Leo*

Department of Radiology, University of Stanford, California, United States

*Author for correspondence:

leo14@us.ac.in

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from complete brain ischemia can only occur for brief ischemic durations of less than about 10 minutes under normal physiological conditions [4]. In areas with incomplete occlusion, this window is extended. For patients with image-proven occlusion of the large cerebral artery in the anterior circulation, current clinical guidelines recommend endovascular clot retrieval (thrombectomy) and intravenous thrombolysis using tissue for reperfusion [5,6].

One of the functions of acute imaging is to distinguish between regions with the potential to be saved and those with irreversible loss of function; this is especially true in the clinic, where stroke onset times may be difficult to determine. Conceptually, stroke affected tissue is divided into a “penumbra,” which is ischemic but still viable if adequate perfusion is successfully restored, and a core area of the severely damaged brain. Clinical imaging assists initial treatment strategies and informs expectations during the acute stage immediately following a stroke [7].

Targeting for subsequent molecular or histological analysis is made possible by preclinical imaging, which also helps to define the evolution of tissue structure and function, both with and without intervention. By identifying tissue with compromised CBF but relatively preserved oxygen utilization as a result of an increased oxygen extraction fraction, Positron Emission Tomography (PET) provided the initial imaging indications of penumbræ. By comparing regional deficits in CBF with loss of GABAergic benzodiazepine receptors, which are abundant in healthy brains and indicate absence of an irreversible neuronal loss due to ischemic injury, nuclear imaging was another method used to define the penumbra. The lead time required for synthesizing radio ligands and the lengthy acquisition times required for sequential scans of each radio ligand make PET unsuitable for acute clinical imaging, despite the fact that it provides the gold standard measurements of CBF, metabolism and neuro receptor densities. Small animal models have limited utility due to their high costs and low spatial resolution [8].

MRI of CBF

A critical parameter in acute stroke and the evaluation of reperfusion efficacy following thrombolysis is regional cerebral blood flow. Due to incomplete recanalization, post-thrombolytic hyperemia, and the “no reflow” phenomenon, the time window of impaired CBF in the periacute phase following thrombolysis may

extend well beyond reperfusion. Flow deficits may persist for several weeks after the recovery stage, according to some clinical and preclinical studies. CBF can be measured using either Arterial Spin Labeling (ASL), which applies a magnetic label to proximal blood in alternating acquisitions and then observes the downstream effects on brain T1-weighted signals or Dynamic Susceptibility Contrast imaging (DSC), which uses tracer-kinetic analysis to analyze the first passage of a bolus of an MRI contrast agent. An alternative to DSC that doesn't use a contrast agent is ASL. Due to an innately frail sign, rehashed signal averaging is expected for ASL to assemble valuable contrast. Although modern implementations of pseudo continuous ASL on clinical scanners are driving a resurgence of interest in this method for a wide variety of clinical perfusion measurements, including stroke, this requirement has limited time critical clinical applications.

Although DSC and ASL are frequently used to define CBF deficits during acute stroke, they have not been used to define CBF deficits over time. However, there is some evidence to suggest that perfusion impairments persist well into the recovery phase. A study of ASL-based perfusion found that CBF decreased by 30% in peri infarct tissue and 15% in the ipsilesional hemisphere on average in a heterogeneous clinical population with a mean of 4 years since stroke imaging; In addition, perfusion deficits were correlated with T2 weighted MRI defined lesion volumes. Perilesional CBF was elevated in sildenafil treated rats for up to 8 weeks in a preclinical comparison with control rats [9].

Angiovascular imaging

Angiogenesis, a process that is thought to be beneficial during recovery in penumbral brain regions but is incompletely understood, is not specifically addressed by any MRI techniques. However, MRI provides techniques for examining the BBB's integrity and determining gross vascular morphology indices, which may be useful for *in vivo* studies of angiogenesis. When gadolinium-based contrast agents are used to evaluate perfusion deficits, MRI signal occurs during the acute phase; these clinical findings may indicate ischemic injury. Due to gadolinium deposition in the cerebrospinal fluid, spatial delineation of BBB dysfunction is non-specific. Leakage is slow and sometimes only apparent on follow up scans because of these agents' relative size. In a similar vein, the permeability of the

blood brain barrier to gadolinium complexes changes significantly in the first few days of some stroke models in rodents and presumably reflects ongoing vascular damage. Increased BBB permeability to gadolinium in penumbral regions for up to 4 weeks has been shown in a few preclinical studies. These findings may indicate vascular remodeling [10].

Conclusion

Acute stroke and studies of stroke recovery using PET only systems suffer from the limitation of PET systems, which can only take one measurement per session. However, targeted molecular probes from concurrent PET complement functional and anatomical MRI. Measurements of glucose metabolism can help interpret suspected diaschisis or luxury perfusion in this context of simultaneous PET/MRI, and radio ligands that target translocator proteins can evaluate neuro inflammation as a possible sign of early lesion progression or late reactive astrocytes. For clinical and basic studies, a variety of combined strategies are possible, such as combining evolving PET methods for imaging angiogenesis with complementary MRI markers or using MRI to track injected cells and PET to demonstrate biological activity.

Imaging oligodendrogenesis may be made easier by the development of new probes that target histone deacetylases. Radio ligand development for novel preclinical and clinical imaging of stroke and other neuropathologies may be sparked by these new research opportunities.

Acknowledgement

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Conflict of Interest

None.

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