Published in final edited form as:
Transl Stroke Res. 2017 February ; 8(1): 1–2. doi:10.1007/s12975-016-0503-5.

Mechanisms, imaging, and therapy in stroke recovery

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Although the majority of phase II/III clinical trials of neuroprotective drugs have failed, recent clinical trials of endovascular recanalization using mechanical thrombectomy were proved effective for acute stroke patients with large vessel occlusions [1–7]. Absolute improvement with endovascular therapy has been found to range between 13.5% to 31%, whereas thrombolytics alone also significantly improve patient functional independence, but to a lesser degree [8]. A meta-analysis provided evidence that for eligible patients with acute ischemic stroke in the setting of large vessel occlusions, outcomes were improved by endovascular intervention combined with medical management, including IV tissue plasminogen activator [9]. Along with recent trends showing a relative reduction in stroke mortality by over 30% [10], these recent advances now make it even more important to dissect the mechanisms of post-stroke recovery and develop efficacious therapies to reduce disability in survivors of acute ischemic stroke.

Profound cellular and biochemical remodeling take place in the brain following an ischemic stroke, and some of these endogenous mechanisms of cerebral plasticity and neurological recovery may be stimulated with behavioral rehabilitation and non-invasive brain stimulation [11–14]. Recovery from stroke is a multifaceted process, and clinical advances continue to be achieved. Current experimental and clinical stroke research focus on the restoration of motor functions [15–20]. By contrast, sensory deficits, cognitive impairment, and depression are less studied, even though these phenomenon would have a major impact on stroke recovery [20]. Neurorehabilitative training has improved clinical recovery of stroke patients in part by augmenting peri-lesional motor plasticity [21–23], but how to adapt these approaches for improving sensory and cognitive recovery remains to be fully investigated. Multiple neuroimaging techniques can now be used to visualize stroke-related structural and functional changes, but more work is required to fully integrate these imaging methods with standard of care to predict and maximize recovery of function [24].

In this Special Issue, we have sought reviews from established experts to explore the frontiers of basic mechanisms, advanced neuroimaging, and potential translational interventions that might be able to promote neurological recovery after ischemic stroke. The first two papers focus on the mechanisms of neurogenesis and axonal repair after stroke. Koh et al [25] discuss ways to stimulate neurogenesis after stroke, and survey ongoing clinical trials focusing on enhancing neurogenesis. Egawa et al [26] discuss the mechanisms underlying axonal degeneration and potential targets that may promote axonal regeneration after brain injury.

The third paper asks whether and how some of these substrates and signals of remodeling after stroke may be quantified with in vivo imaging. In this translational paper, Mandeville et al [27] review the principles and applications of MRI methods in stroke research, including the transition from acute to chronic imaging, preclinical and clinical imaging to determine tissue viability, vascular remodeling, structural connectivity of major white matter tracts, and task-based and resting-state fMRI during the stroke recovery process.

Finally, the last three papers turn to potential therapeutic opportunities for promoting functional recovery after stroke. Cassidy et al [28] summarize the spontaneous and treatment-induced mechanisms driving post-stroke recovery while underscoring the utility of biomarkers that may help guide therapy development. Jeanneret et al [29] review plasticity-induced changes in dendritic spines that are associated with neurological improvement after acute ischemic stroke, with a special emphasis on the role of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) in this process. Lim et al [30] highlight the use of novel biomaterials as an enabling tool and important therapeutic strategy for cell transplantation and drug/protein delivery, and further discuss advances in biomaterial design that can potentially be translated for the stroke patient.

Taken together, these reviews document the current understanding and emerging frontiers of mechanisms and therapeutic strategies that contribute to neuroplasticity and functional recovery after acute ischemic stroke. We hope that the collection of articles in this Special Issue will provide a conceptual framework to guide hypothesis-generation for and future studies of functional recovery following stroke.

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