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EDITORIAL

Recent MRI Advances in Experimental Stroke

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Welcome to this special issue of *Translational Stroke Research*. This special issue focuses on reviewing the development and application of state-of-the-art magnetic resonance imaging (MRI) methodologies to study experimental stroke as reviewed by a panel of leaders in the field. Stroke is the fourth leading cause of death and the leading cause of long-term disability with about 800,000 new or recurrent strokes each year in the USA [1]. More than six million Americans have permanent neurological deficits from stroke, and 71% of these stroke survivors cannot return to work. The incidence of stroke is steadily rising because the conditions that put people at risk for stroke (such as heart disease, diabetes, and obesity) are also steadily on the rise.

MRI is becoming one of the most important diagnostic tools in clinical decision making for the treatment and management of acute and chronic stroke. Diffusion-weighted imaging (DWI) in which image contrast is based on water motion is remarkably sensitive to ischemic brain injury (i.e., within minutes) whereas other conventional imaging techniques such as CT and T1 and T2 MRI fail to detail such injury for at least a few hours [2]. The anatomical mismatch between DWI and perfusion-weighted imaging (PWI) abnormality is indicative of tissue at risk (i.e., approximating the ischemic penumbra) that is potentially salvageable and is the primary target for therapeutic intervention [3].

In addition to DWI and PWI, there are many exciting MRI modalities (such as diffusion tensor imaging, blood–brain barrier permeability imaging, pH MRI, and fMRI and MRI of oxygen extraction, etc.) under development. While these approaches have not yet become routine in stroke clinics, they are being explored and utilized in experimental clinical and animal stroke studies. The data from these multimodal MRI measurements are very rich in physiological information. Many of these approaches are expected to ultimately lead to better characterization of tissue status and prediction of ischemic tissue fate. Together they can also serve as valuable and comprehensive tools to test novel therapeutic strategies.

The goal of this special issue is to review recent development and application of these state-of-the-art MRI techniques in experimental stroke models. It starts with a general introduction of MRI approaches to study stroke by Obenaus and Ashwal [4]. This introduction highlights the broad range of MR imaging modalities that are available to study specific biological processes and evaluation of therapeutic approaches, many of which are detailed in the broad range of articles in this special issue.

Duong [5] describes recent progresses in the development and application of multimodal MRI and image analysis techniques to study ischemic tissue at risk in experimental stroke in rats. The topics covered include: (1) automated clustering analysis of perfusion and diffusion data was used to characterize the spatiotemporal evolution of acute ischemic stroke, (2) the use of blood oxygen level-dependent (BOLD) fMRI of forepaw stimulation and of brief oxygen challenge to probe the perfusion–diffusion mismatch, (3) quantitative predictive models to predict ischemic tissue fate based on acute perfusion and/or diffusion data, and (4) the use of multimodal MRI to investigate the hyperperfusion phenomenon associated with ischemic stroke.

Fisher and Bråtane [6] describe the use of perfusion–diffusion mismatch to evaluate a novel neuroprotective drug. Using diffusion/perfusion MRI in animal stroke models has afforded the opportunity to study the evolution of the ischemic penumbra in exquisite detail. The location and extent of the

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penumbra can be evaluated in real time as can its evolution. Penumbral imaging with these MRI techniques can also be used to evaluate the effects of both thrombolytic and neuroprotective therapy in appropriate animal models.

Ramos-Cabrer and Hoehn [7] review the use of MRI for an innovative therapeutic stroke strategy: the shift from cerebroprotection to regeneration mediated by stem cells. They introduce the complex methodology of labeling stem cells for the longitudinal monitoring for the graft's dynamics. The second part is dedicated to the assessment of cell tracking of the grafted cells, together with those cells from endogenous neurogenesis. In a third section, the role of MR imaging for the therapeutic assessment of regeneration by stem cells is discussed. Here, morphological as well as functional MRI techniques are shown to have an important place.

Dijkhuizen et al. [8] review fMRI and diffusion tensor imaging (DTI) to study brain reorganization after experimental stroke. These MRI approaches enable assessment of longitudinal alterations in neuronal network activity and structure in relation to stroke recovery. Data from recent studies indicate that improvement of sensorimotor function after experimental stroke is associated with wide-ranging changes in functional and structural connectivity within the bilateral sensorimotor network. Functional MRI and DTI of poststroke brain remodeling may therefore provide valuable means for the identification and monitoring of restorative processes that contribute to improvement of functional outcome after ischemic injury.

Leoni et al. [9] describe the application of continuous arterial spin labeling to quantify cerebral blood flow to obtain perfusion territory maps of the major cerebral arteries in spontaneously hypertensive rats and their normotensive Wistar–Kyoto controls under normal and ischemic conditions. They show that the continuous arterial spin labeling technique with a separate radiofrequency coil for arterial spin labeling can be used to map perfusion territory and evaluate collateral perfusion. Following transient ischemia of the right hemisphere, significant and permanent changes in perfusion territories were obtained in both spontaneously hypertensive rats and Wistar–Kyoto. Animals with right dominance presented a larger volume change of the left perfusion territory than animals with left dominance. The data suggest that animals with contralesional dominance primarily safeguard local cerebral blood flow values with small changes in contralesional perfusion territory, while animals with ipsilesional dominance show a reversal of dominance and a substantial increase in contralesional perfusion territory. Their findings show the importance of the collateral circulation in safeguarding ischemic tissue and in improving stroke outcome.

Jiang et al. [10] review blood–brain barrier permeability and susceptibility-weighted MRI measurements and its applications to evaluate ischemic damage during the acute and subacute phases of stroke and vascular remodeling during stroke recovery. This review first discusses the progress, current status, and the future direction in the quantitative blood–brain barrier permeability and susceptibility-weighted MRI measurements and then reviews its applications in predicting and detecting hemorrhage during acute or subacute phase of stroke, as well as the applications in evaluating vascular remodeling during stroke recovery.

An et al. [11] review several MR BOLD methods that have been applied in ischemic stroke. Specifically, they review the underlying hemodynamic pathophysiology that provides the basis of the imaging approaches, followed by a brief introduction of BOLD contrast, and finally the applications of BOLD approaches in ischemic stroke. They place special emphasis on MRI measurements of oxygen extraction fraction and oxygen metabolism associated with ischemic stroke.

Zhou and Van Zijl [12] review the exciting development of pH-weighted MRI. They first outline the principles of this new amide proton transfer MRI methodology for pH imaging. After this, they summarize early results in animal models of ischemia from several groups and discuss the possibility of deriving an acidosis-based ischemic penumbra, based on the difference in areas affected by pH changes and diffusion changes, and a second "penumbra" for benign oligemia. Finally, possible translation to acute stroke in humans is discussed.

And last but not least, Wey et al. [13] review the nonhuman primate stroke imaging literatures. Despite decades of research, no neuroprotective drug has proven to be effective clinically. One widely accepted view to account for this negative outcome is that the rodent stroke model simply does not adequately reflect the complexity and the dynamics of human stroke. The brain organization and vascular circuitry of NHPs are more homologous with humans than the widely used rodent for stroke modeling. The aim of this article is to review the challenges and applications of magnetic resonance imaging studies of NHP stroke models. I am grateful to all of the contributors for their time and efforts.

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