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Multimodal MRI of Nonhuman Primate Stroke

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Abstract

Stroke is the fourth leading cause of death. 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 of human stroke. Recent failures of several high-profile neuroprotective drugs for stroke treatment in phase III clinical trials further underscore the importance of developing adequate animal models for stroke research. The brain organization and vascular circuitry of nonhuman primates (NHPs) are more homologous with humans than the widely used rodent for stroke modeling. The Stroke Therapy Academic Industry Roundtable, a national committee commissioned by the American Heart Association, recommended that clinically relevant NHP stroke models be established for developing and assessing neuroprotective drugs. The aim of this article is to review the challenges and applications of magnetic resonance imaging studies of NHP stroke models.

Keywords

Nonhuman primate; MRI; Perfusion; Diffusion; Functional MRI; MCAO

Introduction

Ischemic stroke is the fourth leading cause of death and the leading cause of long-term disability worldwide [1] constituting a major societal burden. 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. Recent failures of several high-profile neuroprotective drugs in phase III clinical trials further underscore the importance of developing adequate animal models for stroke research. The Stroke Therapy Academic Industry Roundtable [2], a national committee commissioned by the American Heart Association, recommended that clinically relevant nonhuman primate (NHP) stroke models be established for developing and assessing neuroprotective drugs.

With this in mind, a few laboratories have placed a major focus on establishing an interdisciplinary stroke research program based around clinically relevant NHP stroke models paired with innovative high-resolution brain imaging technology. Large NHPs are ideal animal models for studying stroke because one can take advantage of brain organization and vascular circuitry that are more homologous with humans than the widely used rodents for stroke modeling. Additionally, unlike the case for rodents, NHPs allow for the use of well-established behavioral test batteries that assess a wide range of cognitive functions in much the same way we do for clinical patients. Importantly, the imaging technologies developed on the clinical scanners can be seamlessly translated to humans and vice versa.

NHP stroke imaging studies are, however, challenging and sparse because: (1) NHP resources and trained staffs are not widely available, (2) *acute* stroke imaging studies necessitate an expensive imaging facility to be located in very close proximity, and (3) behavioral and cognitive assessment expertise, needed to evaluate stroke NHP for cross comparison with imaging findings, are not widely available. The aim of this article is to review the challenges and applications of magnetic resonance imaging studies of NHP stroke models.

Challenges

There are some significant challenges in carrying out NHP MRI studies in general. The need for animal support, hardware constraints on spatial resolution, signal-to-noise ratio (SNR), and magnetic susceptibility artifacts are some of the major difficulties. These have been described elsewhere [3] and will be briefly reviewed below.

Animal Support—The majority of NHP MRI studies are carried out under anesthesia, which requires veterinary support to provide care for animals during anesthesia and recovery. The common choices of anesthesia are sevoflurane, isoflurane, ketamine, and propofol. The choice of anesthetics and dosages vary depending on the types of MRI experiments (i.e., anatomical MRI versus functional MRI (fMRI)) and the duration of the MRI exams [4]. It is necessary to monitor the physiological status of anesthetized NHPs during MRI experiments. Common physiological parameters include heart rate, respiration rate, arterial oxygen saturation, end-tidal CO₂, blood pressure, and temperature. The monitoring equipment used for these purposes must be MRI compatible, should yield reliable recordings, and should not introduce noise or artifacts in the MR images.

MRI Hardware—MRI scanners specifically designed for imaging primates are sparse and there are only a few in operation to date [5, 6]. Human scanners are however more widely

used for imaging large NHPs (macaque and larger species) [4, 7–9]. The large scanner size and the ease of use for many commonly available MRI protocols make human MRI systems more facile than small-animal imaging systems for translational aspects of NHP imaging research.

The smaller NHP brain volume, compared to human brain volume, make it necessary to acquire images with higher spatial resolution in order to achieve comparable parcellation of anatomical and functional structures [10, 11]. Strong applied magnetic field gradients are necessary to achieve high spatial resolution (i.e., to increase matrix sizes, reduce FOV, and decrease slice thickness). Another factor that makes high spatial resolution NHP MRI challenging is the available SNR. To achieve optimal SNR, radiofrequency (RF) coils should have the maximum possible filling factor—that is the RF coils should be the smallest possible to cover the organs of interest. A limitation of NHP MRI studies on human scanners is that RF coils of different sizes may not be readily available. The few standard human RF coils may not be ideal for various NHP sizes. Thus, centers with a substantial NHP MRI research portfolio may consider developing their own RF coil fabrication capability.

NHP Stroke Models

The majority of NHP stroke models are based on the occlusion of the middle cerebral artery (MCAO) [12, 13]. There are two major categories of NHP stroke model (for review see [14]). The first category uses transorbital, retro-orbital, or intracranial techniques to gain access to target vessel(s). The retro-orbital and intracranial approaches are technically more demanding compared to transorbital approach, and could become problematic when performing MRI because both require craniotomy. Transorbital approach does not require head surgery, but the removal of one eye is a major surgery and doing so prohibits behavioral evaluation of the visual field and spatial deficits. In addition, transorbital approach usually required long occlusion duration to cause sufficient lesion sizes. The second category uses an endo-vascular method. An endovascular model is ideally suited for monitoring the ischemia longitudinally using MRI, because it is the least invasive and avoids these limitations, although this model and its reproducibility require validation [12, 13]. NHP stroke models involved other vessels either with or without MCAO have also been reported but are less frequently used [15, 16].

MRI of NHP Stroke

Few MRI studies have focused on experimental NHP stroke, and most studies used conventional MRI (such as T2 and FLAIR) to characterize the non-acute phase of injury at a single time point [17–19], which is often at endpoint to quantify lesion volume. NHP stroke studies perform MRI beyond anatomical protocols are sparse. A MRS NHP stroke study has been reported [20]. Multimodality MRI includes anatomical, diffusion, and/or perfusion MRI to longitudinally image NHP stroke is only reported recently [13, 21]. The major NHP stroke imaging studies are reviewed below.

Diffusion MRI—A few studies employed diffusion tensor imaging to characterize longitudinal changes of diffusion parameters in NHP stroke [13, 21, 22]. Liu et al. measured

apparent diffusion coefficient (ADC) and fractional anisotropy (FA) changes in permanent and transient MCAO in macaques, and compared with T2 and histology to determine endpoint lesion size [21]. This study established the temporal profile of diffusion changes in NHP stroke. It also concluded that reperfusion accelerated the changes of diffusion parameters when compared with permanent stroke. ADC decreases within lesion territory were apparent in the acute phase. Compared with other studies, ADC pseudo-normalized at ~8 days in marmosets [22] and ~10 days in macaques [21]. In human studies, the time of normalized ADC varied substantially but a mean of ~10–14 days was reported [21, 23, 24]; while in rodent studies, a diminished ADC was often found much earlier (~1–4 days) after stroke. These studies showed that temporal evolution of diffusion parameters, although these depended on occlusion durations, in NHP stroke are more similar to humans and were distinct from rodent [13, 21, 22].

Chin et al. carried out serial diffusion tensor imaging in transient MCAO in two macaques and compared diffusion parameters with motor function measurements [25]. The authors reported transient decreases in FA values of affected motor pathways, and suggested the recovery of FA correlate accompanying gradual motor recovery in the chronic phase.

Small NHPs, such as marmosets, have also been used in NHP stroke MRI studies [22, 26–28]. Although marmosets are more evolutionarily distant from human compared with Old World primates (e.g., macaques and baboons), they are relatively easy to handle, which is advantageous for surgical procedures and behavioral training and evaluations [22, 26–28]. Marshall et al. [27] reported detailed behavioral assessments in marmosets who underwent permanent MCAO together with MRI on the day of stroke and in the chronic stage (3, 10, and 20 weeks). Although the authors showed a time difference in motor and spatial functional recovery, they suggested that MRI taken shortly after a stroke might be more useful for lesion volume prediction.

Freret et al. [26] developed a new stroke model using intraluminal thread in common marmosets. They studied both permanent and transient (3 h) MCAO and used MRI to define lesion volumes (8 days after MCAO) in a sub-group of marmosets to correlate with behavioral measurements. They found that although lesion volumes are comparable between the two groups, marmosets that underwent reperfusion exhibited fewer neurologic and functional impairments compared to permanently occluded animals [26]. Using the same stroke model, a follow-up study performed by the same group, incorporated three sequential MRI examinations in the acute (1 h), sub-acute (8 days), to chronic phase (45 days), when changes in T2 and ADCs were being evaluated [22]. Again, a lesion evolution closer to what is observed in humans relative to rodents was shown.

Perfusion MRI—Regions with mismatch between blood flow and metabolism, i.e., the region of “misery perfusion” [29], was the imaging-based definition of the ischemic penumbra which is considered the potential salvageable tissue. Imaging tissue metabolism is not straightforward using MRI. During the acute phase of stroke, the area of cerebral blood flow (CBF) deficit is usually larger than the initial diffusion deficit. The difference in the size and extent of the enhancing regions visible in perfusion-weighted and diffusion-weighted images is referred to as the “perfusion–diffusion mismatch”. This mismatch has

been shown to approximate the potentially salvageable ischemic penumbra [30]. The spatiotemporal evolution of the ischemic lesion during the acute phase is a highly dynamic process as the mismatch gradually decreases over time [31, 32], and thus represents a rapidly moving target for treatment. The perfusion–diffusion mismatch has been widely observed in humans [30, 33, 34], but similar observations have not been demonstrated in NHPs. The spatiotemporal dynamics of the mismatch and the tissue viability threshold in NHP stroke models remain to be investigated before NHP stroke being used to evaluate treatment efficacy with MRI. Perfusion MRI using dynamic susceptibility contrast has been performed in NHP stroke, and lesion volumes defined by perfusion parameters were reported [35].

Wey et al. implemented perfusion MRI using arterial spin labeling, which is ideally suited for serial MRI within one imaging session, and demonstrated the spatial-temporal characteristics of perfusion–diffusion mismatch in baboon stroke [13, 36]. An advantage of using baboon is that it offers a larger brain compared to macaques making them more amenable to MRI studies. Wey et al. reported reperfusion salvaged substantial of the perfusion–diffusion mismatch tissue [13]. The mismatch volume was found progressively decreased for up to 6 h post-occlusion, in contrast to mismatch volumes in rodent models that lasted up to 3 h post-occlusion [37]. In humans, the perfusion–diffusion mismatch is often detected up to 6–12 h after stroke onset, and the frequency of detection decreased with time [38]. Consistent with previous serial diffusion MRI studies in NHP stroke which reported temporal profiles of diffusion parameters concord more with humans than rodents, the spatial-temporal dynamics of perfusion–diffusion mismatch appear to be more similar to humans than rodents as well.

Discrepancies of the temporal profiles among species highlights the importance of using NHP stroke models with serial MRI to establish tissue signature of lesion and evaluate treatment efficacy. Overall, these results from serial MRI in NHP stroke demonstrate that stroke can be reproducibly studied in a clinically more relevant animal model in which the precise stroke onset is known. NHP stroke model combined with clinically relevant MRI approaches could positively impact stroke research.

Sodium MRI—Sodium–potassium ion pump failure due to impaired energy metabolism is a detrimental step in the ischemic cascade. Sodium MRI techniques have been used to monitor the changes of tissue sodium concentration (TSC) in NHP stroke [39–41]. It was shown that the TSC increases linearly during the period of occlusion [41] and this increase stopped after reperfusion [40, 41]. Because of this linearity, the mechanisms underlying TSC accumulation in ischemia is hypothesized to be related to the loss of ion homeostasis and is affected by level of remaining CBF [40, 42]. Interestingly, due to the linear increases of TSC with individual differences in the rate of TSC accumulations, and the confirmation of most rapid increases occurs in the ischemic core (as confirmed with histology) [42], the potential use of TSC as a biomarker to estimate stroke onset has been suggested [42, 43]. These proof-of-concept studies showed the feasibility of sodium MRI. Further improvements on the imaging techniques and quantification approach might be proven useful in stroke research. In addition, serial sodium MRI in combination with other clinical

proton MRI methodologies (such as perfusion and diffusion MRI) would help better understand the ischemic evolution.

Resting-State fMRI—Liu et al. have carried out a resting-state fMRI study in NHP stroke. They reported that the spontaneous fMRI signal fluctuation altered in the peri-infarct area and suggested that resting-state fMRI might provide additional information to diffusion and perfusion MRI [44]. From a network perspective, any physiological and pathological processes could affect the underlying intra- or inter-network interactions. Resting-state fMRI provides a means to investigate the functional connectivity between brain regions [45, 46]. Using resting-state functional connectivity fMRI to characterize cortical plasticity in chronic stroke might offer unique insights regarding within-network (intra-hemispherical and inter-hemispherical) and between-networks interactions and their relationship with behavioral outcomes [47].

Conclusions

Non-invasive MRI can provide clinically relevant structural, physiological, and functional data in a single setting at very high spatiotemporal resolution in NHPs. Given that numerous neuroprotective drugs have shown positive results on rodent stroke models whereas none has proven to be effective clinically, large NHP stroke models could be important for assessing efficacy of neuroprotective drugs before clinical trials. Moreover, the imaging technologies developed on the clinical scanners for NHPs can be directly applied to humans.

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