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Topical Review

The Potential for Advanced Magnetic Resonance Neuroimaging Techniques in Pediatric Stroke Research

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ABSTRACT

BACKGROUND: This article was written to provide clinicians and researchers with an overview of a number of advanced neuroimaging techniques in an effort to promote increased utility and the design of future studies using advanced neuroimaging in childhood stroke. The current capabilities of advanced magnetic resonance imaging techniques provide the opportunity to build on our knowledge of the consequences of stroke on the developing brain. These capabilities include providing information about the physiology, metabolism, structure, and function of the brain that are not routinely evaluated in the clinical setting. **METHODS:** During the Proceedings of the Stroke Imaging Laboratory for Children Workshop in Toronto in June 2015, a subgroup of clinicians and imaging researchers discussed how the application of advanced neuroimaging techniques could further our understanding of the mechanisms of stroke injury and repair in the pediatric population. This subgroup was established based on their interest and commitment to design collaborative, advanced neuroimaging studies in the pediatric stroke population. **RESULTS:** In working toward this goal, we first sought to describe here the magnetic resonance imaging techniques that are currently available for use, and how they have been applied in other stroke populations (e.g., adult and perinatal stroke). **CONCLUSIONS:** With the continued improvement in advanced neuroimaging techniques, including shorter acquisition times, there is an opportunity to apply these techniques to their full potential in the research setting and learn more about the effects of stroke in the developing brain.

Keywords: pediatric, stroke, MRI, neuroimaging

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Introduction

Advances in neuroimaging have been central to the improved recognition, diagnosis, investigation, and management of stroke in children.[1] However, further progress in these areas is hindered by a significant gap in our understanding of the mechanisms of injury and repair in the developing brain. Advanced magnetic resonance imaging (MRI) techniques can be applied to address these gaps with the goal of developing mechanism-targeted interventions that are critically needed in the pediatric stroke population. MRI is particularly appealing in pediatric stroke research, in that it offers a noninvasive, nonionizing method for imaging various properties of the brain including physiology, metabolism, anatomy, structure, and function (Table lists these advanced MRI techniques and what they measure).

In an effort to begin the development of imaging-based research strategies in pediatric ischemic stroke, a subgroup of clinicians and researchers gathered during the Proceedings of the Stroke Imaging Laboratory for Children Workshop in Toronto in June 2015. This article was written to provide an overview of the magnetic resonance (MR) neuroimaging techniques discussed in this workshop specifically with a focus on techniques that are currently available and how they have been applied in other stroke populations (e.g., adult and perinatal stroke) as a first step toward developing imaging guided research in pediatric stroke.

Blood oxygen level–dependent imaging

Blood oxygen level–dependent (BOLD) imaging has been used in a number of ways to study the function of the brain. These include mapping the responsiveness of the cerebrovasculature, the network connections of the brain at rest (in the absence of a task), and the functional networks of the brain (in response to a task).

BOLD imaging can detect relative changes in blood oxygenation that is believed to be a surrogate measure of changes in cerebral blood flow. The magnetic susceptibility of blood changes dramatically when it becomes deoxygenated because of the presence of paramagnetic deoxyhemoglobin in red cells. Thus deoxygenated blood acts as a natural intravascular contrast agent that induces a greater signal loss in the surrounding tissue compared with fully oxygenated blood. This phenomenon is known as the BOLD contrast and is well suited for noninvasive brain activation studies.

Cerebrovascular reactivity

Cerebrovascular reactivity (CVR) is a measure of cerebral blood flow change in response to a global vasoactive stimulus and serves as a stress test to interrogate the dilatory capacity of the cerebral vasculature. The combination of carbon dioxide (CO_2) challenging with BOLD imaging is a well-established method for assessing regional differences in CVR.[2,3] CO_2 mediates vasoreactivity at the arterioles (also termed resistance vessels) and increases both blood volume and blood flow without affecting the metabolic rate of oxygen.[4,5] When imaged with BOLD MRI, CO_2 increases MRI signal and CVR can be quantified as percent MR signal change per unit stimuli (Fig 1). Although the changes quantified using BOLD imaging do reflect underlying changes in cerebral blood flow, it must be emphasized that BOLD imaging is an indirect measure of CVR as the method is only sensitive to changes in deoxygenated hemoglobin induced by changes in cerebral blood flow.

Other stimuli such as acetazolamide have also been used to quantify CVR, but the application of CO_2 has several advantages, specifically in pediatric subjects. The stimulus is safe, easy to apply, and can be standardized between subjects by dividing the percent change in MRI signal by the change in arterial or end-tidal CO_2 levels (the latter are easier to measure). Various methods for administering a CO_2 breathing challenge can be implemented, depending on the desired level of control. Simplistic approaches like breath holding do not require any equipment and rely on the subject's ability to follow specific respiratory maneuvers. More complex methods involve closely calibrated gases fed into custom breathing masks to enforce accurate targeting

TABLE.
Advanced Magnetic Resonance Neuroimaging Techniques: What They Measure and Length of Acquisition

Technique	What it Measures	Acquisition Time* (Minutes)	Postprocessing Needed (Yes/No)†
BOLD—CVR	Cerebral vessel function in response to a vasoactive stimulus (CO_2)	~8	Yes
Task-based fMRI	Task oriented neural activity (function)	~5-20	Yes
Resting-state fMRI	Connectivity of brain networks	~5-15	Yes
Arterial spin labeling	Cerebral blood flow (without the use of exogenous contrast agent)	~4-10	Yes
Dynamic contrast-enhanced MRI	Blood-brain barrier permeability (contrast agent needed)	~4-5	Yes
Diffusion tensor imaging	White matter fiber orientation	~4-15	Yes
Diffusion kurtosis imaging	Kurtosis: non-normative diffusion capable of quantifying heterogeneity in microstructure of white and gray matter	~11	Yes
Neurite orientation dispersion and density imaging	Intracellular and extracellular water diffusion	~25	Yes
Vessel wall imaging	Vascular wall pathology (contrast agent needed)	~10-20	No
3D isotropic	Morphometry of brain anatomy	~5-10	Yes
Magnetic resonance spectroscopy	Cellular metabolites in the brain	~4-20	Yes
Oxygen metabolism (MR-COMI)	Quantification of cerebral metabolic index of oxygen	~3-10	Yes

Abbreviations:
BOLD = Blood oxygen level–dependent imaging
CVR = Cerebrovascular reactivity
fMRI = functional magnetic resonance imaging
MR-COMI = magnetic resonance derived cerebral metabolic oxygen index
* Approximations: these acquisition times include a wide range to account for variability in technique subtypes and implementations.
† Refers to postprocessing of acquired images.