## Title

Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop



## Authors

Dlamini, Nomazulu
Wintermark, Max
Fullerton, Heather
et al.

## Publication Date

2017-04-01

## DOI

10.1016/j.pediatrneurol.2017.01.006

Peer reviewed

Pediatric Neurology 69 (2017) 3–10

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Commentary

# Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children Workshop

**Nomazulu Dlamini MD, PhD [a,*], Max Wintermark MD [b], Heather Fullerton MD [c,d], Stephen Strother PhD [e], Wayne Lee MSc [a], Bruce Bjornson MD [f,g], Kristin P. Guilliams MD [h,i], Steven Miller MD [a], Adam Kirton MD [j,k], Christopher G. Filippi MD [l,m], Alexandra Linds MSc [a], Rand Askalan MD, PhD [a], Gabrielle deVeber MD [a]**

[a] *Division of Neurology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada*
[b] *Division of Neuroradiology, Department of Radiology, Stanford University, Stanford, California*
[c] *Department of Neurology, University of California, San Francisco, San Francisco, California*
[d] *Department of Pediatrics, University of California, San Francisco, San Francisco, California*
[e] *Department of Medical Biophysics, Rotman Research Institute at Baycrest, University of Toronto, Toronto, Ontario, Canada*
[f] *Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada*
[g] *Developmental Neurosciences and Child Health, Child and Family Research Institute, Vancouver, British Columbia, Canada*
[h] *Division of Pediatric Neurology, Department of Neurology, Washington University in St. Louis, St. Louis, Missouri*
[i] *Division of Critical Care Medicine, Department of Pediatrics, Washington University in St. Louis, St. Louis, Missouri*
[j] *Department of Pediatrics, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[k] *Department of Clinical Neurosciences, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[l] *Department of Radiology, Northwell Health, Manhasset, New York*
[m] *Department of Neurology, University of Vermont Medical Center, Burlington, Vermont*

ABSTRACT

On June 5, 2015 the International Pediatric Stroke Study and the Stroke Imaging Laboratory for Children cohosted a unique workshop focused on developing neuroimaging research in pediatric stroke. Pediatric neurologists, neuroradiologists, interventional neuroradiologists, physicists, nurse practitioners, neuropsychologists, and imaging research scientists from around the world attended this one-day meeting. Our objectives were to (1) establish a group of experts to collaborate in advancing pediatric neuroimaging for stroke, (2) develop consensus clinical and research magnetic resonance imaging protocols for pediatric stroke patients, and (3) develop imaging-based research strategies in pediatric ischemic stroke. This article provides a summary of the meeting proceedings focusing on identified challenges and solutions and outcomes from the meeting. Further details on the workshop contents and outcomes are provided in three additional articles in the current issue of Pediatric Neurology.

***Keywords:*** pediatric, stroke, neuroimaging, MRI, diffusion, perfusion, cerebrovascular reactivity

Pediatr Neurol 2017; 69: 3-10



## Introduction

Pediatric arterial ischemic stroke (AIS), defined by focal infarction within a vascular territory, occurs in one in 3500 live births and 1 to 3 per 100,000 children per year.[1,2] Pediatric AIS remains one of the top ten causes of death

*Article History:*
Received September 30, 2016; Accepted in final form January 6, 2017

* Communications should be addressed to: Dr. Dlamini; Stroke Program; Division of Neurology; The Hospital for Sick Children; 555 University Avenue; Toronto, Canada.
*E-mail address:* nomazulu.dlamini@sickkids.ca

0887-8994/$ – see front matter © 2017 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2017.01.006

and lifelong disability in childhood. The socioeconomic impact of pediatric stroke is significant.[3-5]

Brain injury because of AIS results from arterial occlusion, critical decrease in regional perfusion, and focal brain tissue ischemia. Within the focal ischemic zone complex molecular and tissue changes occur. After acute ischemic infarction, at least some functional recovery occurs related to compensatory brain rewiring and repair. Characterization of these mechanisms from infancy to adult years is an important area of research. Emerging research-based imaging techniques can further expand our understanding of the mechanisms underlying focal ischemic injury and repair within the developing brain. An enhanced understanding of these mechanisms will ultimately help us to develop novel treatment approaches aimed at minimizing injury and enhancing mechanisms of repair, thereby improving outcomes in pediatric AIS (Table).

Although similar clinical challenges (timely detection and targeted therapy) exist in AIS across pediatric and adult patients, differences in mechanisms of stroke pathogenesis, injury, and repair likely exist. Clinical management relies upon appropriate neuroimaging to provide specific diagnosis, etiological classification, and patient selection for possible therapies. Yet imaging strategies that are feasible in adults present specific challenges in infants and children. This workshop was convened to harness opportunities for developing systematic and collaborative research to address the unique aspects of imaging in the pediatric stroke population.

The Stroke Imaging Laboratory for Children (SILC) cohosted the meeting in collaboration with the International Pediatric Stroke Study.[6] SILC was recently established at the Hospital for Sick Children Research Institute to advance imaging research in pediatric stroke. Leveraging the latest imaging technology, SILC aims to employ synergistic neuroimaging techniques to provide new insights into pediatric stroke. Consistent with these aims, Part I of the workshop consisted of slide presentations that emphasized (1) acute practical imaging needs and solutions; (2) imaging of acute pathogenesis; (3) stroke lesion delineation; (4) imaging stroke impact: recovery and plasticity; and (5) building a collaborative network. Part II of the day consisted of breakout sessions with working groups focused on three main objectives: (1) establishing a group of experts to collaborate in advancing imaging; (2) developing consensus-based clinical and research magnetic resonance imaging (MRI) protocols; and (3) developing and sharing imaging-based research strategies in pediatric AIS. A major outcome of the workshop was the development of four complementary articles designed to address the aforementioned objectives. The current article presents the overview of the meeting and the framework from which the other more specific articles were developed.[7-10]

**TABLE.**
Imaging Stroke Mechanisms

| Cerebral Artery Wall Pathology | Wall Imaging MRI |
|---|---|
| Cerebral artery lumen (e.g., occlusion) | MRA |
| Perfusion drop | Perfusion imaging, CVR, SWI |
| Brain tissue cell death | DWI, DKI |
| Recanalization | MRA |
| Reperfusion | Perfusion imaging, CVR |
| Blood-brain barrier breakdown | Gadolinium enhancement |
| Hemorrhagic conversion of bland infarct | SWI |
| Neuronal salvage | ?? |
| Reperfusion injury | DCE |
| Plasticity and repair | fMRI, MEG |
| Rewiring | DTI |

Abbreviations:
CVR = Cerebrovascular reactivity
DCE = Dynamic contrast enhancement
DKA = Diffusion kurtosis imaging
DTI = Diffusion tensor imaging
DWI = Diffusion-weighted imaging
fMRI = Functional magnetic resonance imaging
MEG = Magnetoencephalography
MRA = Magnetic resonance angiogram
MRI = Magnetic resonance imaging
SWI = Susceptibility-weighted imaging
?? = Requires further research

## Pediatric stroke: Overview, clinical challenges, and imaging solutions

Part I of the day consisted of presentations that outlined the challenges and potential imaging solutions to timely diagnosis, treatment selection, and recognition of the pathogenesis of pediatric AIS in the acute setting.

### *Imaging for stroke diagnosis—the acute infarct and penumbra*

The differential diagnosis of acute onset focal neurological symptoms in childhood is broad, posing a challenge to accurate and timely diagnosis of pediatric AIS.[11,12] Specific imaging confirmation of stroke is necessary. In adults, the differential diagnosis of acute focal deficits is narrow and cranial computed tomography (CT) imaging to rule out bleeding is the standard initial imaging modality. However, CT has limited sensitivity for pediatric AIS, missing 50% to 80% of lesions verified by MRI.[13] Exposure to ionizing radiation is an additional consideration in the developing brain.[14] Accordingly, MRI has emerged as the modality of choice for the initial diagnosis of pediatric AIS. Diffusion-weighted imaging (DWI) utilizes the diffusion properties of water to interrogate cellular integrity and injury.[15,16] Animal and human studies have shown that ischemic injury and restricted diffusion become evident on diffusion-weighted MRI when cerebral blood flow (CBF) falls below 20 mL per 100 g/minute. Thus diffusion restriction on MRI in pediatric AIS is meant to represent irreversibly infarcted tissue or the ischemic core. Outside the ischemic core, where CBF reduction may not have reached this critical threshold, DWI remains normal but perfusion-weighted imaging (PWI) is abnormal. This finding is the neuroimaging equivalent of the penumbra, which is potentially viable, but vulnerable tissue that may provide a therapeutic target for recanalization and neuroprotective care in acute ischemic stroke.[17,18]

Identification of patients most likely to benefit from recanalization and neuroprotection care requires perfusion imaging. The main MR perfusion techniques used in adults, including T2* dynamic susceptibility contrast imaging and T1 dynamic contrast enhancement, require the use of gadolinium contrast agents. The invasive nature of the contrast

administration (high volume bolus in small venous channels), risk of anaphylaxis, nephrotoxicity, slow clearance and, in the case of repeated administrations, retention of gadolinium contrast in the brain[19-21] pose significant challenges to their application in the pediatric population.

Dr. A. Vossough and Dr. M. Rivkin presented new opportunities of assessing brain perfusion in the pediatric stroke population as follows:

(1) Arterial spin labeling (ASL) perfusion harnesses the properties of blood water protons to provide an endogenous contrast agent. Clinically available commercial ASL sequences are not yet validated in childhood as a result of the technical challenges of studying steno-occlusive disease in this developmentally heterogenous group. However, ASL offers significant promise for improving our understanding and treatment of acute pediatric stroke and has recently been successfully used in children with moyamoya.[10,22]
(2) High-spatial-resolution three-dimensional gradient echo (GRE) MR sequence using susceptibility-weighted imaging (SWI) is another promising approach to measure perfusion. This sequence has been used in healthy and asphyxiated newborns,[23] and recently, for assessing penumbra, in neonates with stroke.[24] In AIS, severe reduction of cerebral perfusion is associated with an increased deoxyhemoglobin-to-oxyhemoglobin ratio because of a compensatory increase in the oxygen extraction fraction.[25] Regional variations in the SWI appearance of hypointense veins draining ischemic brain (with higher concentration of deoxyhemoglobin) and normally perfused brain (with lower concentration of deoxyhemoglobin) have been demonstrated in adults[26-28] and children[29,30] with AIS. Further exploration of this modality in the pediatric population is required.[8,9]

*Imaging assessment for directing hyperacute and acute therapies*

Dr. Catherine Amlie-Lefond presented on how imaging can inform patient selection for hyperacute reperfusion therapies and highlighted important imaging outcomes. Reperfusion therapies, with endovascular devices and thrombolytic agents, are the mainstay of treatment for selected, eligible adult patients treated within 6 hours from onset of AIS. Animal studies of cell death, apoptosis, and autophagy demonstrate age-related similarities and differences in vulnerability and resilience to ischemic injury.[31,32] These findings emphasize the opportunity for reperfusion and neuroprotection in pediatric AIS. However, the absence of safety data with endovascular devices presents a significant barrier to their use in young children with AIS stroke.[31,33]

One complication of thrombolysis is hemorrhagic transformation of the ischemic infarct, with an associated increased likelihood of severe neurological deficit and poor outcome in children.[34,35] The use of MR imaging data to aid patient selection for thrombolysis has been associated with improved outcomes and reduced risks from acute thrombolysis in adults. A number of these approaches, relevant to the pediatric population, were presented in the workshop:

(1) Large volume (more than 2/3 of the middle cerebral artery territory) infarcts are associated with an increased risk of hemorrhagic transformation. Hence, rapid determination of the acute lesion volume is desirable. Simple visual assessment of infarct volume is feasible using the Alberta Stroke Program Early Computed Tomographic scoring method,[36] which predicts functional outcome and hemorrhage risk in patients who are candidates for intravenous thrombolysis. The scoring system has subsequently been applied to pediatric AIS and to MRI.[36-38] Drs. T. Schmah and R. Filippi presented novel and validated semiautomated volumetric tools for potential future application to children. However, recognized limitations include lesion segmentation and the need to preset apparent diffusion coefficient values, the latter being more problematic in the setting of pediatric acute ischemic stroke.[38]
(2) Large baseline PWI lesion volumes, known as “malignant” low perfusion patterns (PWI [Tmax greater than 8 seconds] volume of more than 85 mL as the optimal definition of the malignant profile), are associated with higher rates of thrombolysis-related parenchymal hemorrhage and severe disability or death.[39] In comparison, reperfusion therapy in patients with “target” mismatch patterns has significantly favorable clinical outcomes.[40,41]Therefore characterization of pediatric PWI/DWI patterns could improve the selection of ideal pediatric AIS candidates for future trials of recanalization treatments.
(3) Dr. N. Dlamini presented on MR-based qualitative and quantitative methods of assessing cerebrovascular reactivity (CVR) using clinically available T2* gradient echo sequences. The brain relies on autoregulation as an important mechanism for maintaining CBF despite variations in systemic blood pressure. CVR compares cerebral tissue perfusion at baseline and during hypercapnic challenge to evaluate regional cerebral autoregulation. CVR is an important marker of cerebrovascular reserve that has been shown to predict ischemic risk in adults.[42,43] Studies of CVR in the acute and chronic phases after stroke can provide information regarding failure of regional and global autoregulatory capacity and individual patient susceptibility to ischemic injury, supporting patient selection for acute and subacute reperfusion strategies. The CVR technique has been validated in both adult and pediatric populations and provides a novel opportunity for adoption into clinical practice.[44-46]
(4) Dr. A. Kassner described the benefits of blood-brain barrier (BBB) imaging in stroke. Adult imaging studies of BBB integrity have demonstrated an association between BBB disruption and an increased risk of hemorrhagic transformation.[47] Recombinant tissue plasminogen activator (tPA) itself further compromises BBB integrity, potentially contributing to increased hemorrhagic transformation and adverse patient outcomes.[48] No longitudinal data exist on BBB permeability changes from the first few hours to the first days after acute ischemic stroke.[48,49] Animal studies have identified imatinib as a potential neuroprotective agent to preserve the BBB after acute ischemic stroke, which could result in the extension of the therapeutic window in pediatric stroke.[10,50]

*Imaging for stroke etiology and classification*

Determining the etiology of stroke in childhood is a major challenge. Classification systems have been developed to better predict risk and recurrence, as well as guide management.[51] All of these systems are highly dependent on the nature and quality of the clinical information in addition to brain and vascular imaging.[52-54]

Intracranial arteriopathy is the leading cause of pediatric AIS and confers a fivefold increase in stroke recurrence risk.[55,56] Transient cerebral arteriopathy, intracranial arterial dissection, and moyamoya represent the common arteriopathies of childhood, which typically involve the arteries of the internal carotid bifurcation. Available luminal MR or CT angiography techniques are unable to reliably distinguish across arteriopathy subtypes. Dr. D Mikulis shared his experience of vessel wall imaging (VWI) using high-resolution 3 Tesla MRI with gadolinium in adults. VWI has been shown to differentiate various arterial pathologies, through distinct patterns of contrast enhancement.[57,58] However, the few available reports in children are limited to case studies. The use of contrast and the interpretation of vessel wall contrast enhancement remain as challenges to the implementation of contrast-based VWI in childhood.[59] Further exploration of noncontrast and nonenhanced wall imaging is required.[60] Simple angiographic patterns of arterial anatomy, such as arterial tortuosity, may also provide clues to the nature of arteriopathic stroke in childhood.[61,62]

*Imaging impact of stroke and plasticity*

In the final presentations of Part I, we explored imaging predictors of outcome, recovery, and plasticity described in the following sections.

*Imaging predictors of outcome*

In children with AIS, sensorimotor and cognitive outcomes vary widely and this variability remains relatively unexplained. Kirton et al. previously reported on a qualitative approach to the classification of presumed perinatal ischemic stroke based on visually matching the infarct distribution to known vascular territories. They demonstrated the ability of the classification system to predict outcome.[63] Infarct volume is another imaging biomarker of outcome.[64] However, the measurement of chronic infarct volumes is technically challenging and time consuming given the need for manual segmentation. Dr. N. Stence et al. reported on an exploratory method of estimating volume of perinatal AIS on chronic imaging that can compensate for the changes in brain volume in early infancy. The technique compares healthy ipsilesional versus contralesional hemispheric tissue volumes using manual segmentation methods. They demonstrated that this indirect method accurately estimates perinatal infarct volumes more accurately than direct methods.[65]

Automated methods exist that allow for lesion classification, volume assessment, tracking of longitudinal change, and potentially automatic prediction of outcome in children and neonates with AIS and other brain lesions.[66-68] However, few have been systematically studied in the pediatric population. Dr. R. Filippi presented a novel computer assisted volumetric method, which markedly simplifies automated volume measurement of stroke lesions, and has been developed and validated with clinical outcome severity in pediatric acute infarcts.[69] Additional improvements in automated stroke lesion detection and measurement will be realized with better methods of registration and segmentation of brain lesions.

Dr. A. Kirton presented on clinically relevant imaging biomarkers in brain locations remote from the stroke lesion. Diaschisis is a term used to describe the focal depression of neurological function in a brain region that is distant from the original site of injury but anatomically connected to it by fiber tracts.[70,71] Ipsilesional acute Wallerian degeneration (also termed “preWallerian degeneration”) appearing as restricted diffusion MRI signal within descending corticospinal tracts has been correlated with chronic motor deficits in neonatal,[72-74] childhood,[75,76] and adult stroke.[77-81] Subtle coexisting restricted diffusion has also been noted in the contralesional corticospinal tract within the pons.[75] However, the pathological basis and significance of the latter finding is yet unknown.[76] Such early outcome predictors may inform stroke recovery mechanisms and aid in patient selection for clinical trials.

*Imaging of stroke recovery and plasticity*

Understanding the basis of neuroplasticity and after stroke sensorimotor recovery can help inform prognosis, rehabilitation therapies, and future trials in the chronic phase of pediatric acute ischemic stroke. Neuroplasticity refers to the ability of the brain to respond and modify its structure and function after injury. Concepts of “young age plasticity advantage” or the “Kennard-effect”[82-84] versus “early vulnerability”[85] have recently merged into the concept of a recovery continuum across maturation between plasticity and vulnerability in pediatric acute ischemic stroke.[86] Several conventional and novel neuroimaging techniques can interrogate the underlying plasticity processes, such as MR diffusion techniques and functional MRI.

MR diffusion techniques allow for the assessment of tissue microstructure integrity. MR-based diffusion tensor imaging (DTI) allows for the assessment of white matter microstructure integrity and tractography. DTI studies in children with perinatal and childhood ischemic stroke have demonstrated a relationship between lower fractional anisotropy values and poor motor outcome in children highlighting the structure-function relationship in this group.[87,88]

Alternative diffusion imaging approaches and models, including intravoxel incoherent motion (IVIM) and multishell high angular resolution diffusion imaging[89] coupled with multicompartment models (e.g., neurite orientation dispersion and density imaging (NODDI)) have also shown promise for the assessment of acute stroke. Such approaches make it possible to assess fiber orientation and both intracellular and free water diffusion in a single voxel. Preliminary work in adult stroke patients suggests that NODDI metrics may detect changes in stroke regions not otherwise detectable using traditional diffusion imaging approaches.[90]

The application of functional MRI (fMRI) and magnetoencephalopgraphy (MEG) imaging techniques to inform our understanding of recovery and plasticity after stroke in

childhood was summarized in presentations by Dr. T. Domi and Dr. D. Cheyne, respectively. Functional MRI measures the regional blood oxygen level–dependent (BOLD) signal as an indirect measure of regional neuronal activity. fMRI compares different brain regions at rest—resting state fMRI—or during a task—task-based fMRI. Resting state fMRI is able to provide detailed spatial information about the baseline extent of neuronal activity within cerebral networks by measuring the coherent fluctuations of fMRI signals (functional connectivity).[91] Adult stroke studies have reported on the predictive value of fMRI in evaluating altered ipsilesional and contralesional brain network integrity underlying clinical motor and cognitive deficits.[92,93] Studies of network reorganization in children after stroke are few.[94,95] However, studies using fMRI to evaluate hand function in children with remote stroke by Domi et al.[96] demonstrated a high correlation between motor deficit and greater asymmetry in fMRI activations. Differences in sensorimotor reorganization after ischemic injury may impact neuroplasticity and response to rehabilitative interventions.[97,98]

Although fMRI is unable to provide direct information about network activity, other electrophysiologic measures can do so. Transcranial magnetic stimulation can provide information about activational remapping of the sensorimotor cortex after a lesion and has been used in pediatric stroke. However, spatial information is limited.[99,100] MEG can be used to detect cortical oscillatory activity and can localize frequency specific brain activity with high temporal and spatial resolution providing information about neural network reorganization, plasticity, and repair after stroke. Perilesional, ipsilesional, and contralesional alterations in frequency and amplitude of sensorimotor cortical excitability correlate with clinical outcome in adult stroke.[101,102] Multimodal imaging studies have demonstrated bilateral alterations in somatosensory evoked fields in children with hemiplegic cerebral palsy[103,104] and disruption of thalamocortical projections.[105] Studies using MEG in this population have shown modulated somatosensory evoked fields in the affected hemisphere after cast-therapy intervention[106] and Juenger et al.[97] demonstrated differential neuroplasticity and outcomes in children with stroke after constraint-induced movement therapy. MEG studies examining abnormal cortical excitability and short-term plasticity in the somatosensory system in children with after stroke dystonia are ongoing.

*Building collaborative networks*

The International Pediatric Stroke Study (IPSS) arose from the need to establish a large collaborative community of experts with an interest in pediatric stroke.[107] To date, the IPSS accounts for 57 active centers (total 219 since 2003) and more than 5000 infants and children with ischemic stroke are enrolled in the primary IPSS study. The IPSS has generated 18 clinical and epidemiologic peer-reviewed articles to date, which have highlighted the range of challenges in diagnosis and management, and the need for further systematic research including treatment trials. Several IPSS substudies funded by the National Institute of Neurological Disorders and Stroke and other agencies are ongoing.

The "Vascular Effects of Infection in Pediatric Stroke"[108] study used the IPSS network to enroll more than 350 children with AIS and age-matched controls, collecting all clinically obtained brain and vascular imaging on more than 300 stroke cases from 22 centers. Central storage, classification, and imaging review at University of California, San Francisco has enabled more accurate classification of stroke etiology and arteriopathy subtypes.[108] In addition, the resultant imaging library became a valuable resource, allowing new analytic techniques to be retrospectively applied, such as a method for measuring arterial tortuosity using MRA data.[61] However, imaging data in vascular effects of infection in pediatric stroke (VIPS) study were limited by variability in the clinical stroke imaging protocols at the 37 different enrolling sites.

Multicenter imaging collaborations and future trials present additional challenges beyond dealing with large databases of imaging studies. They include the need for a quality assurance process to ensure anonymization of the data and an appropriate bioinformatics infrastructure with support to electronically transfer, store, and analyze multidimensional data. The varying imaging software and technology can also pose challenges to multicenter imaging and data analysis. Biological samples for genomic and proteomic analysis can provide additional relevant data in pediatric AIS research potentially correlating with imaging markers of mechanisms of injury and recovery. Essential to the highly collaborative network is the domain expertise of the various teams in software systems and programming, mathematics and statistics, neuroscience, and medicine. The development of integrated neuroinformatics for translation research relies heavily on the neuroimaging workflow pathways with the potential to use multitier preprocessing pipelines for image review, interpretation, and analysis. Alternatively, data-driven approaches using a neuroinformatics systems approach to big data analysis do not require understanding of mechanisms and can be used to augment clinical decision making. Finally, building a collaborative network also relies on policies designed to both safeguard privacy and security and to define how data ownership and access will be managed and reflected in authorship. Both are necessary conditions for potential contributors to be comfortable sharing their data.

There are many recent examples of consortia that have tackled these issues in specific disease domains. Such examples often come with extensive documentation, infrastructure, and associated open source software. Beyond Vascular Effects of Infection in Pediatric Stroke, other relevant consortia include the Biomedical Informatics Network (BIRN) and their approach to multisite neuroimaging studies (http://www.birncommunity.org/); different database approaches considered for adult stroke by the Canadian Centre for Stroke Recovery; and for multiple disease domains and data modalities, development of the Brain-CODE data repository and related governance structures by the Ontario Brain Institute. IPSS and SILC imaging repositories and other multicenter imaging collaborations will need to carefully assess such relevant prior experience and available infrastructure as they develop.

## Breakout Sessions

Part II of the day consisted of breakout sessions with working groups focused on the three aforementioned main

objectives: (1) establishing a group of experts to collaborate in advancing imaging; (2) developing consensus-based clinical and research MRI protocols; and (3) developing and sharing imaging-based research strategies in pediatric AIS.

Since this first meeting, the group met at the American Society for Neuroradiology 54th Annual Meeting, further solidifying the collaborative network initiated at the initial workshop and formalizing linkages within the IPSS Neuroimaging Subgroup. The immediate common goal of the IPSS and SILC laboratory was to develop standardized imaging protocols so that clinically obtained studies could be more readily compared across institutions. Hence, the publication of the two clinical guidelines in this issue[8,9] and the research imaging article[10] pursuant to the initial meeting is an important first step toward this goal. Finally, Brain Canada recently funded a platform support grant titled "Canadian Paediatric Stroke Imaging Research Platform: Harnessing an International Focus" based at SILC to pilot a prospective imaging study across an initial five pilot sites with a view to further expansion of multisite prospective research imaging in the next phase. The initial study will enroll 90 children with acute AIS. Participants will be imaged with many of the research techniques described previously during acute, subacute (three months), and chronic (12 months) phases. SILC will serve as a hub for imaging data and grant operations.

## Conclusions and next steps

We report the proceedings of the first cohosted IPSS and SILC workshop focused on developing neuroimaging research in pediatric stroke. We brought together a group of experts who during the course of the day highlighted the challenges of diagnosis and management of pediatric AIS, and the opportunities to address these challenges using conventional and novel imaging techniques. Including this, four articles will be published as a result of the proceedings of this workshop, and the research imaging collaborative network established.

Large multicenter research networks, which include the IPSS are now well-established and provide the foundation for fostering neuroradiologists, stroke neurologists, and imaging scientists to collaborate and add multiple dimensions to the existing data repository, including imaging. Such infrastructure and collaborations will improve the clinical care of pediatric stroke through the creation of consensus-based imaging protocols and hypothesis-driven research protocols to further elucidate the pathophysiology and mechanisms of focal injury and recovery in the developing brain.

The authors thank Gabrielle's Ride for funding this one-day workshop (http://www.gabriellesride.com/).

## References


1. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. *Stroke*. 2009;40:3415-3421.
2. Mallick AA, Ganesan V, Kirkham FJ, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. *Lancet Neurol*. 2014;13:35-43.
3. deVeber G, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. *J Child Neurol*. 2000;15:316-324.
4. Fullerton HJ, Chetkovich DM, Wu YW, Smith WS, Johnston SC. Deaths from stroke in US children, 1979 to 1998. *Neurology*. 2002;59:34-39.
5. Lo W, Gordon AL, Hajek C, et al. Pediatric stroke outcome measure: predictor of multiple impairments in childhood stroke. *J Child Neurol*. 2014;29:1524-1530.
6. Fullerton HJ, deVeber G. Practice variability in the treatment of childhood acute ischemic stroke: Results of the International Pediatric Stroke Study. *Stroke*. 2007;38:485.
7. Dlamini N, Wintermark M, Fullerton H, et al. Harnessing Neuroimaging Capability in Pediatric Stroke: Proceedings of the Stroke Imaging Laboratory for Children (SILC) Workshop. *Pediatric Neurol*. 2017;69:3-10. http://dx.doi.org/10.1016/j.pediatrneurol.2017.01.006.
8. Lee S, Mirsky DM, Beslow LA, et al. Pathways for Neuroimaging of Neonatal Stroke. *Pediatric Neurol*. 2017;69:11-23. http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.008.
9. Mirsky DM, Beslow LA, Amlie-Lefond C, et al. Pathways for Neuroimaging of Childhood Stroke. *Pediatric Neurol*. 2017;69:37-48. http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.004.
10. Domi T, Vossough A, Stence NV, et al. The Potential for Advanced Neuro MRI Techniques in Pediatric Stroke Research. *Pediatric Neurol*. 2017;69:24-36. http://dx.doi.org/10.1016/j.pediatrneurol.2016.12.015.
11. Srinivasan J, Miller SP, Phan TG, Mackay MT. Delayed recognition of initial stroke in children: need for increased awareness. *Pediatrics*. 2009;124:e227-e234.
12. Rafay MF, Pontigon AM, Chiang J, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. *Stroke*. 2009;40:58-64.
13. deVeber GA. Delays in the timely diagnosis of stroke in children. *Nat Rev Neurol*. 2010;6:64-66.
14. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med*. 2007;357(22):2277-2284.
15. Moseley ME, Cohen Y, Mintorovitch J, et al. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. *Magn Reson Med*. 1990;14:330-346.
16. AE B, S W. Magnetic resonance imaging of acute stroke. *J Cerebr Blood Flow Metab*. 1998;18:583-609.
17. Busza AL, Allen KL, King MD, van Bruggen N, Williams SR, Gadian DG. Diffusion-weighted imaging studies of cerebral ischemia in gerbils. Potential relevance to energy failure. *Stroke*. 1992;23:1602-1612.
18. Gadian DG, Calamante F, Kirkham FJ, et al. Diffusion and perfusion magnetic resonance imaging in childhood stroke. *J Child Neurol*. 2000;15:279-283.
19. Levin JM, Kaufman MJ, Ross MH, et al. Sequential dynamic susceptibility contrast MR experiments in human brain: residual contrast agent effect, steady state, and hemodynamic perturbation. *Magn Reson Med*. 1995;34:655-663.
20. Kanda T, Ishii K, Kawaguchi H, Kitajima K, Takenaka D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270:834-841.
21. Kanda T, Oba H, Toyoda K, Kitajima K, Furui S. Brain gadolinium deposition after administration of gadolinium-based contrast agents. *Jpn J Radiol*. 2016;34:3-9.
22. Blauwblomme T, Lemaitre H, Naggara O, et al. Cerebral Blood Flow Improvement after Indirect Revascularization for Pediatric Moyamoya Disease: A Statistical Analysis of Arterial Spin-Labeling MRI. *AJNR Am J Neuroradiol*. 2016;37:706-712.
23. Boudes E, Gilbert G, Leppert IR, et al. Measurement of brain perfusion in newborns: pulsed arterial spin labeling (PASL) versus pseudo-continuous arterial spin labeling (pCASL). *Neuroimage Clin*. 2014;6:126-133.
24. Watson CG, Dehaes M, Gagoski BA, Grant PE, Rivkin MJ. Arterial Spin Labeling Perfusion Magnetic Resonance Imaging Performed in Acute Perinatal Stroke Reveals Hyperperfusion Associated With Ischemic Injury. *Stroke*. 2016;47:1514-1519.
25. Derdeyn CP, Yundt KD, Videen TO, Carpenter DA, Grubb Jr RL, Powers WJ. Increased oxygen extraction fraction is associated with

prior ischemic events in patients with carotid occlusion. *Stroke*. 1998;29:754-758.
26. Hermier M, Nighoghossian N. Contribution of susceptibility-weighted imaging to acute stroke assessment. *Stroke*. 2004;35:1989-1994.
27. Kesavadas C, Thomas B, Pendharakar H, Sylaja PN. Susceptibility weighted imaging: does it give information similar to perfusion weighted imaging in acute stroke? *J Neurol*. 2011;258:932-934.
28. Kao HW, Tsai FY, Hasso AN. Predicting stroke evolution: comparison of susceptibility-weighted MR imaging with MR perfusion. *Eur Radiol*. 2012;22:1397-1403.
29. Chalian M, Tekes A, Meoded A, Poretti A, Huisman TA. Susceptibility-weighted imaging (SWI): a potential non-invasive imaging tool for characterizing ischemic brain injury? *J Neuroradiol*. 2011;38:187-190.
30. Meoded A, Poretti A, Tekes A, Huisman TAGM. Clinical Vignette: Role of Susceptibility-Weighted Imaging in Predicting Stroke Evolution Neurographics. 1 2013;3:159-163(155)
31. Xu M, Zhang HL. Death and survival of neuronal and astrocytic cells in ischemic brain injury: a role of autophagy. *Acta Pharmacol Sin*. 2011;32:1089-1099.
32. Vexler ZS, Sharp FR, Feuerstein GZ, et al. Translational stroke research in the developing brain. *Pediatr Neurol*. 2006;34(6):459-463.
33. Buompadre MC, Andres K, Slater LA, et al. Thrombectomy for Acute Stroke in Childhood: A Case Report, Literature Review, and Recommendations. *Pediatr Neurol*; 2016.
34. Bruno CJ, Beslow LA, Witmer CM, et al. Haemorrhagic stroke in term and late preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2014;99:F48-F53.
35. Kirton A, Schecter T, Brandao L, et al. Hemorrhagic transformation of arterial ischemic stroke in children. *Stroke*. 2007;38:581.
36. Barber PA, Hill MD, Eliasziw M, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76:1528-1533.
37. Beslow LA, Vossough A, Dahmoush HM, et al. Modified Pediatric ASPECTS Correlates with Infarct Volume in Childhood Arterial Ischemic Stroke. *Front Neurol*. 2012;3:122.
38. Kosior RK, Lauzon ML, Steffenhagen N, Kosior JC, Demchuk A, Frayne R. Atlas-based topographical scoring for magnetic resonance imaging of acute stroke. *Stroke*. 2010;41:455-460.
39. Mlynash M, Lansberg MG, De Silva DA, et al. Refining the definition of the malignant profile: insights from the DEFUSE-EPITHET pooled data set. *Stroke*. 2011;42:1270-1275.
40. Lansberg MG, Lee J, Christensen S, et al. RAPID automated patient selection for reperfusion therapy: a pooled analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) Study. *Stroke*. 2011;42:1608-1614.
41. Fisher M, Albers GW. Advanced imaging to extend the therapeutic time window of acute ischemic stroke. *Ann Neurol*. 2013;73:4-9.
42. Gupta A, Chazen JL, Hartman M, et al. Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke*. 2012;43:2884-2891.
43. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. *JAMA*. 2000;283:2122-2127.
44. Han JS, Mikulis DJ, Mardimae A, et al. Measurement of Cerebrovascular Reactivity in Pediatric Patients With Cerebral Vasculopathy Using Blood Oxygen Level-Dependent MRI. *Stroke*. 2011;42:1261-1269.
45. Bright MG, Murphy K. Reliable quantification of BOLD fMRI cerebrovascular reactivity despite poor breath-hold performance. *Neuroimage*. 2013;83:559-568.
46. Leung J, Kim JA, Kassner A. Reproducibility of cerebrovascular reactivity measures in children using BOLD MRI. *J Magn Reson Imaging*. 2016;43:1191-1195.
47. Kassner A, Roberts T, Taylor K, Silver F, Mikulis D. Prediction of hemorrhage in acute ischemic stroke using permeability MR imaging. *AJNR Am J Neuroradiol*. 2005;26:2213-2217.
48. Kassner A, Roberts TP, Moran B, Silver FL, Mikulis DJ. Recombinant tissue plasminogen activator increases blood-brain barrier disruption in acute ischemic stroke: an MR imaging permeability study. *AJNR Am J Neuroradiol*. 2009;30:1864-1869.
49. Bang OY, Buck BH, Saver JL, et al. Prediction of hemorrhagic transformation after recanalization therapy using T2*-permeability magnetic resonance imaging. *Ann Neurol*. 2007;62:170-176.
50. Merali Z, Leung J, Mikulis D, Silver F, Kassner A. Longitudinal assessment of imatinib's effect on the blood-brain barrier after ischemia/reperfusion injury with permeability MRI. *Transl Stroke Res*. 2015;6:39-49.
51. Amlie-Lefond C, Chan AK, Kirton A, et al. Thrombolysis in acute childhood stroke: design and challenges of the thrombolysis in pediatric stroke clinical trial. *Neuroepidemiology*. 2009;32:279-286.
52. Wraige E, Pohl KR, Ganesan V. A proposed classification for subtypes of arterial ischaemic stroke in children. *Dev Med Child Neurol*. 2005;47:252-256.
53. Sebire G, Fullerton H, Riou E, deVeber G. Toward the definition of cerebral arteriopathies of childhood. *Curr Opin Pediatr*. 2004;16:617-622.
54. Bernard TJ, Manco-Johnson MJ, Lo W, et al. Towards a consensus-based classification of childhood arterial ischemic stroke. *Stroke*. 2012;43:371-377.
55. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. *Circulation*. 2006;114:2170-2177.
56. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. *Pediatrics*. 2007;119:495-501.
57. Kuker W, Gaertner S, Nagele T, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. *Cerebrovasc Dis*. 2008;26:23-29.
58. Swartz RH, Bhuta SS, Farb RI, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. *Neurology*. 2009;72:627-634.
59. Mineyko A, Kirton A, Ng D, Wei XC. Normal intracranial periarterial enhancement on pediatric brain MR imaging. *Neuroradiology*. 2013;55:1161-1169.
60. Mandell DM, Shroff M. On MR imaging of the intracranial vessel wall. *Can J Neurol Sci*. 2011;38:4-5.
61. Wei F, Diedrich KT, Fullerton HJ, et al. Arterial Tortuosity: An Imaging Biomarker of Childhood Stroke Pathogenesis? *Stroke*. 2016;47:1265-1270.
62. Dlamini N, Freeman JL, Mackay MT, et al. Intracranial dissection mimicking transient cerebral arteriopathy in childhood arterial ischemic stroke. *J Child Neurol*. 2011;26:1203-1206.
63. Kirton A, deVeber G, Pontigon AM, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol*. 2008;63:436-443.
64. Ganesan V, Ng V, Chong WK, Kirkham FJ, Connelly A. Lesion volume, lesion location, and outcome after middle cerebral artery territory stroke. *Arch Dis Child*. 1999;81:295-300.
65. Stence NV, Mirsky DM, Weitzenkamp D, et al. Acute Infarct Volume in Perinatal Stroke Can Be Accurately Estimated by Measuring Residual Uninfarcted Tissue on Follow-up MRI. Paper presented at: Stroke 2015.
66. Hope TM, Seghier ML, Leff AP, Price CJ. Predicting outcome and recovery after stroke with lesions extracted from MRI images. *Neuroimage Clin*. 2013;2:424-433.
67. Gillebert CR, Humphreys GW, Mantini D. Automated delineation of stroke lesions using brain CT images. *Neuroimage Clin*. 2014;4:540-548.
68. Cheng I, Miller SP, Duerden EG, et al. Stochastic process for white matter injury detection in preterm neonates. *Neuroimage Clin*. 2015;7:622-630.
69. Filippi CG, El-Ali AM, Miloushev VZ, Chow DS, Guo X, Zhao B. Computer-assisted volumetric measurement of core infarct volume in pediatric patients: feasibility for clinical use and development of quantitative metrics for outcome prediction. *AJNR Am J Neuroradiol*. 2015;36:789-794.
70. Finger S, Koehler PJ, Jagella C. The Monakow concept of diaschisis: origins and perspectives. *Arch Neurol*. 2004;61:283-288.
71. Monakow CV. *Die lokalisation im grosshirn und der abbau der funktion durch kortikale herde*. Wiesbaden,: J. F. Bergmann; 1914.
72. de Vries LS, van der GJ, van Haastert IC, Groenendaal F. Prediction of outcome in new-born infants with arterial ischaemic stroke using diffusion-weighted magnetic resonance imaging. *Neuropediatrics*. 2005;36:12-20.

73. Kirton A, Shroff M, Visvanathan T, deVeber G. Quantified corticospinal tract diffusion restriction predicts neonatal stroke outcome. *Stroke*. 2007;38:974-980.
74. McKinstry RC, Miller JH, Snyder AZ, et al. A prospective, longitudinal diffusion tensor imaging study of brain injury in newborns. *Neurology*. 2002;59:824-833.
75. T.Domi, deVeber G, Shroff M, Kouzmitcheva E, MacGregor DL, Kirton A. Corticospinal tract pre-wallerian degeneration: a novel outcome predictor for pediatric stroke on acute MRI. *Stroke*. 2009;40:780-787.
76. Jones KC, Hawkins C, Armstrong D, et al. Association between radiographic Wallerian degeneration and neuropathological changes post childhood stroke. *Dev Med Child Neurol*. 2013;55:173-177.
77. Pendlebury ST, Blamire AM, Lee MA, Styles P, Matthews PM. Axonal injury in the internal capsule correlates with motor impairment after stroke. *Stroke*. 1999;30:956-962.
78. Pineiro R, Pendlebury ST, Smith S, et al. Relating MRI changes to motor deficit after ischemic stroke by segmentation of functional motor pathways. *Stroke*. 2000;31:672-679.
79. Riley JD, Le V, Der-Yeghiaian L, et al. Anatomy of stroke injury predicts gains from therapy. *Stroke*. 2011;42:421-426.
80. Schaechter JD, Perdue KL, Wang R. Structural damage to the corticospinal tract correlates with bilateral sensorimotor cortex reorganization in stroke patients. *Neuroimage*. 2008;39:1370-1382.
81. Zhu LL, Lindenberg R, Alexander MP, Schlaug G. Lesion load of the corticospinal tract predicts motor impairment in chronic stroke. *Stroke*. 2010;41:910-915.
82. Ballantyne AO, Spilkin AM, Hesselink J, Trauner DA. Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain*. 2008;131(Pt 11):2975-2985.
83. Dennis M, Spiegler BJ, Juranek JJ, Bigler ED, Snead OC, Fletcher JM. Age, plasticity, and homeostasis in childhood brain disorders. *Neurosci Biobehav Rev*. 2013;37(10 Pt 2):2760-2773.
84. Kennard MA. Age and other factors in motor recovery from precentral lesions in monkeys. *Am J Physiol*. 1936;115:138-146.
85. Max JE, Bruce M, Keatley E, Delis D. Pediatric stroke: plasticity, vulnerability, and age of lesion onset. *J Neuropsychiatry Clin Neurosci*. 2010;22:30-39.
86. Anderson V, Spencer-Smith M, Wood A. Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*. 2011;134(Pt 8):2197-2221.
87. Domi T, Mikulis D, McAndrews M, Bells S, Shroff M, deVeber G. Correlation of Fractional Anisotropy (FA) Measures and Functional MRI Activations (fMRI) of Pediatric Stroke Patients Following Variable Hand Recovery. Paper presented at: ANNALS OF NEUROLOGY 2009.
88. van der Aa NE, Verhage CH, Groenendaal F, et al. Neonatal neuroimaging predicts recruitment of contralesional corticospinal tracts following perinatal brain injury. *Dev Med Child Neurol*. 2013;55:707-712.
89. Ratnayake WM, Chardigny JM, Wolff RL, Bayard CC, Sebedio JL, Martine L. Essential fatty acids and their trans geometrical isomers in powdered and liquid infant formulas sold in Canada. *J Pediatr Gastroenterol Nutr*. 1997;25:400-407.
90. Adluru G, Gur Y, Anderson JS, Richards LG, Adluru N, DiBella EV. Assessment of white matter microstructure in stroke patients using NODDI. *Conf Proc IEEE Eng Med Biol Soc*. 2014;2014:742-745.
91. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature*. 2001;412:150-157.
92. He BJ, Snyder AZ, Vincent JL, Epstein A, Shulman GL, Corbetta M. Breakdown of functional connectivity in frontoparietal networks underlies behavioral deficits in spatial neglect. *Neuron*. 2007;53:905-918.
93. Park CH, Chang WH, Ohn SH, et al. Longitudinal changes of resting-state functional connectivity during motor recovery after stroke. *Stroke*. 2011;42:1357-1362.
94. Dinomais M, Groeschel S, Staudt M, Krageloh-Mann I, Wilke M. Relationship between functional connectivity and sensory impairment: red flag or red herring? *Hum Brain Mapp*. 2012;33:628-638.
95. Kornfeld S, Delgado Rodriguez JA, Everts R, et al. Cortical reorganisation of cerebral networks after childhood stroke: impact on outcome. *BMC Neurol*. 2015;15:90.
96. Domi T, Mikulis D, McAndrews MP, deVeber G. Structural Integrity of the Corticospinal Tract Correlated with the Degree of Hand Recovery in Pediatric Patients Following Stroke. *Stroke*. 2012;43(Suppl 1). A4033-A4033.
97. Juenger H, Kuhnke N, Braun C, et al. Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study. *Dev Med Child Neurol*. 2013;55:941-951.
98. Walther M, Juenger H, Kuhnke N, et al. Motor cortex plasticity in ischemic perinatal stroke: a transcranial magnetic stimulation and functional MRI study. *Pediatr Neurol*. 2009;41:171-178.
99. Kirton A. Can noninvasive brain stimulation measure and modulate developmental plasticity to improve function in stroke-induced cerebral palsy? *Semin Pediatr Neurol*. 2013;20(2):116-126.
100. Garvey MA, Mall V. Transcranial magnetic stimulation in children. *Clin Neurophysiol*. 2008;119:973-984.
101. Laaksonen K, Kirveskari E, Makela JP, et al. Effect of afferent input on motor cortex excitability during stroke recovery. *Clin Neurophysiol*. 2012;123:2429-2436.
102. Rossiter HE, Boudrias MH, Ward NS. Do movement-related beta oscillations change after stroke? *J Neurophysiol*. 2014;112:2053-2058.
103. Nevalainen P, Pihko E, Maenpaa H, Valanne L, Nummenmaa L, Lauronen L. Bilateral alterations in somatosensory cortical processing in hemiplegic cerebral palsy. *Dev Med Child Neurol*. 2012;54:361-367.
104. Pihko E, Nevalainen P, Vaalto S, et al. Reactivity of sensorimotor oscillations is altered in children with hemiplegic cerebral palsy: A magnetoencephalographic study. *Hum Brain Mapp*. 2014;35:4105-4117.
105. Papadelis C, Ahtam B, Nazarova M, et al. Cortical somatosensory reorganization in children with spastic cerebral palsy: a multimodal neuroimaging study. *Front Hum Neurosci*. 2014;8:725.
106. Sutcliffe TL, Gaetz WC, Logan WJ, Cheyne DO, Fehlings DL. Cortical reorganization after modified constraint-induced movement therapy in pediatric hemiplegic cerebral palsy. *J Child Neurol*. 2007;22:1281-1287.
107. Group TIPSS. Establishing a Multinational Research Network in Paediatric Stroke: The International Paediatric Stroke: The International Paediatric Stroke Study. *Ann Neurol*. 2006;60:S149.
108. Wintermark M, Hills NK, deVeber GA, et al. Arteriopathy diagnosis in childhood arterial ischemic stroke: results of the vascular effects of infection in pediatric stroke study. *Stroke*. 2014;45:3597-3605.