RESEARCH ARTICLE

Imaging functional motor connectivity in hemiparetic children with perinatal stroke

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Abstract

Perinatal stroke causes lifelong disability, particularly hemiparetic cerebral palsy. Arterial ischemic strokes (AIS) are large, cortical, and subcortical injuries acquired near birth due to acute occlusion of the middle cerebral artery. Periventricular venous infarctions (PVI) are smaller, subcortical strokes acquired prior to 34 weeks gestation involving injury to the periventricular white matter. Both stroke types can damage motor pathways, thus, we investigated resulting alterations in functional motor networks and probed function. We measured blood oxygen level dependent (BOLD) fluctuations at rest in 38 participants [10 arterial patients (age = 14.7 ± 4.1 years), 10 venous patients (age = 13.5 ± 3.7 years), and 18 typically developing controls (TDCs) (age = 15.3 ± 5.1 years)] and explored strength and laterality of functional connectivity in the motor network. Inclusion criteria included MRI-confirmed, unilateral perinatal stroke, symptomatic hemiparetic cerebral palsy, and 6–19 years old at time of imaging. Seed-based functional connectivity analyses measured temporal correlations in BOLD response over the whole brain using primary motor cortices as seeds. Laterality indices based on mean z-scores in lesioned and nonlesioned hemispheres explored laterality. In AIS patients, significant differences in both strength and laterality of motor network connections were observed compared with TDCs. In PVI patients, motor networks largely resembled those of healthy controls, albeit slightly weaker and asymmetric, despite subcortical damage and hemiparesis. Functional connectivity strengths were not related to motor outcome scores for either stroke group. This study serves as a foundation to better understand how resting-state fMRI can assess motor functional connectivity and potentially be applied to explore mechanisms of interventional therapies after perinatal stroke.

KEYWORDS

perinatal stroke, functional connectivity, motor networks, resting-state fMRI, cerebral palsy, pediatric

1 | INTRODUCTION

Perinatal stroke is an umbrella term for a focal brain injury that occurs as a result of a cerebral vascular accident between 20 weeks gestation and the 28th postnatal day (Nelson, 2007; Raju, Nelson, Ferriero, & Lynch, 2007). The period of greatest risk for stroke is the first week of life, with more than 1 in 3,500 live births incurring perinatal stroke (Raju et al., 2007). Perinatal stroke can be further characterized based on the timing of the stroke: (1) fetal ischemic stroke which is

diagnosed antenatally, (2) neonatal ischemic stroke which is diagnosed after birth, and (3) presumed perinatal ischemic stroke which is diagnosed after the 28th postnatal day, but presumed to have occurred perinatally. Motor deficits are the most common morbidity associated with perinatal stroke, resulting in hemiplegic cerebral palsy, which for the purpose of our study is defined as any child with a unilateral motor deficit and imaging confirmed stroke (Kirton, 2013; Wu et al., 2004). The effects of perinatal stroke last for decades, and most survivors endure other neurodevelopmental morbidities in addition to

motor deficits (DeVeber, MacGregor, Curtis, & Mayank, 2000; Golomb, 2001; Lee et al., 2005; Mercuri et al., 2004; Sreenan, Bhargava, & Robertson, 2000). As a result, affected children, their families, and the health care system continue to struggle with the burden of perinatal stroke (Taylor et al., 1996).

There are two main types of perinatal stroke: arterial ischemic stroke (AIS) and periventricular venous infarction (PVI) (Kirton, DeVeber, Pontigon, Macgregor, & Shroff, 2008; Kirton & deVeber, 2009). AIS are typically large, cortical and subcortical injuries acquired near birth due to acute occlusion of the middle cerebral artery (Figure 1a) (Kirton et al., 2008, 2011). In contrast, PVIs are smaller, subcortical strokes acquired prior to 34 weeks gestation (Kirton et al., 2008; Takanashi, Barkovich, Ferriero, Suzuki, & Kohno, 2003). PVI injures the periventricular white matter secondary to impaired medullary venous drainage after a germinal matrix hemorrhage (Figure 1b) (Kirton & Wei, 2010; Takanashi, Tada, Barkovich, & Kohno, 2005). Both stroke types typically damage primary components of the developing motor system, resulting in lifelong motor deficits and physical disability.

Human neurophysiology and neuroimaging findings have been combined with animal data to construct models of developmental motor plasticity following early unilateral injury (Eyre, 2007; Kirton, 2017; Staudt, 2007). Injured upper motor neurons may be less able to compete for synapse formation in the contralateral anterior horn (of the spinal cord) that typically occurs during early motor development. The result is a persistence of ipsilateral connections from the contralesional motor cortex, the role of which is increasingly defined in perinatal stroke (Zewdie, Damji, Ciechanski, Seeger, & Kirton, 2016). In fact, the contralesional primary motor cortex (M1) has been targeted in several recent positive clinical trials of noninvasive neuromodulation for perinatal stroke hemiparesis (Gillick, Friel, Menk, & Rudser, 2016; Kirton et al., 2017, 2016). This demonstrates the translational relevance of advancing such models, but also highlights important limitations in our understanding of underlying developmental plasticity.

It has been well-established that adult strokes of the motor network are associated with altered interhemispheric interactions, which has guided many modern therapeutic neuromodulation approaches (Carter et al., 2010; Thiel & Vahdat, 2015; Wang et al., 2010). Using transcranial magnetic stimulation (TMS), we have recently demonstrated that alterations in interhemispheric interactions are also clinically relevant in children with perinatal stroke (Eng, Zewdie, Ciechanski, Damji, & Kirton, 2017). The ability to assess interhemispheric functional connections between the motor cortices and beyond, at baseline and following intervention, would be a powerful addition to understanding developmental plasticity after perinatal stroke.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a promising solution to this problem (Biswal, Yetkin, Haughton, & Hyde, 1995). By assessing the temporal cross-correlation of blood oxygenation level dependent (BOLD) fMRI signals from distinct brain regions during participant rest, one can infer the strength of functional connections between regions of a brain network (called functional connectivity) (Grefkes et al., 2010; Zhang & Raichle, 2010). In adult stroke, rs-fMRI has demonstrated brain reorganization in the motor and other functionally specific systems and suggests how interventions such as noninvasive brain stimulation may act to change these motor networks to promote recovery (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). A recent rs-fMRI study of children with perinatal stroke observed alterations of the default mode network in AIS patients, but not PVI patients, which correlated with cognitive assessment scores (Ilves et al., 2016). Such evidence supports feasibility and suggests rs-fMRI may be a valuable tool to better understand motor network connectivity to identify therapeutic targets and mechanisms in perinatal stroke and other forms of cerebral palsy. In the present study, we conducted a controlled rs-fMRI study of hemiparetic children with perinatal stroke to characterize alterations in motor network functional connectivity. We hypothesized that interhemispheric motor connectivity would be reduced after perinatal stroke,

FIGURE 1 T1-weighted anatomical imaging for a typical AIS (a) and PVI (b) patient. C. Lesion overlay maps for ten participants with arterial (AIS) strokes illustrating lesion location and extent. Shown are heat maps corresponding to the number of patients that have a lesion in that area overlaid on axial slices from a standard template in MNI space (MNI152). AIS, arterial ischemic stroke; MNI, Montreal Neurological Institute. Images are presented in neurological convention (i.e., right hemisphere is on the right side)

the degree of which would be associated with stroke type (AIS worse than PVI) and clinical assessment of function.

2 | METHODS

2.1 | Subjects

Perinatal stroke participants were recruited through the Alberta Perinatal Stroke Project (APSP), a population-based research cohort based at the Alberta Children's Hospital consisting of over 200 children with clinical and imaging confirmed perinatal stroke (Cole et al., 2017). Inclusion criteria consisted of MRI-confirmed, unilateral perinatal stroke, symptomatic hemiparetic cerebral palsy, term birth, and were 6–19 years old at the time of imaging. Participants were excluded if they had other neurological disorders unrelated to perinatal stroke, multifocal or bilateral stroke, severe hemiparesis (Manual Abilities Classification System (MACS) level 5, that is, does not handle objects with the affected limb and has severely limited ability to perform even simple actions, requiring total assistance), severe spasticity, severe developmental delays, unstable epilepsy, contraindications to MRI, or had received botox, orthopedic surgery, constraint therapy, brain stimulation, or other modulatory therapy in the past 6 months. The typically developing control (TDC) group was recruited through posted advertisements around the Alberta Children's Hospital and consisted of healthy children in the same age range with no neurological disorders, neuroactive medications, or contraindications to MRI. Written parental consent and participant assent were obtained. This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary.

2.2 | Neuroimaging

MR imaging was conducted using a GE MR750w 3 Tesla MRI scanner with a 32-channel receive head coil (GE Healthcare, Waukesha, WI). T_1 -weighted images were acquired in the axial plane using a 3D fast spoiled gradient echo (FSPGR BRAVO) sequence [166 slices, no gap, voxel size = 1 mm isotropic, matrix = 256×256 , repetition time (TR) = 8.5 ms, echo time (TE) = 3.2 ms]. T_2 -weighted images were also acquired for co-registration purposes [axial plane, 36 slices, no gap, voxel size = 0.45×0.45 mm, slice thickness = 3.6 mm, matrix = 512×512 , TR/TE = 6,794/80 ms].

Resting-state and task-based fMRI data were acquired using a gradient-recalled echo, echo planar imaging (GRE-EPI) sequence, consisting of 150 and 137 T_2^* -weighted whole brain volumes, respectively (36 contiguous slices, slice thickness = 3.6 mm, TR/TE = 2,000/30 ms, duration ~5–6 min). During rs-fMRI acquisition, participants were instructed to lie still, stay awake, and think about nothing in particular while focusing on a fixation cross.

Task-based fMRI was performed by stroke patients only in order to localize the primary motor cortex (M1) within each hemisphere for subsequent placement of the regions of interest (ROI) required for rs-fMRI analysis. The task was a block design consisting of finger tapping interleaved with periods of rest. Participants viewed a red, centrally presented fixation cross (rest block, 24 s in duration) and tapped a

button with the index finger on their nondominant hand synchronously with the cross when it changed color from red to green (task block, tapping frequency ~1 Hz, 12 s in duration). Eight blocks of rest were interleaved with seven blocks of task, totaling 276 s. The task was then repeated with the dominant hand.

2.3 | fMRI analysis

Analysis of all fMRI data (i.e., both task and resting-state) was carried out using the FMRIB Software Library (FSL; version 5.0) (Smith et al., 2004; Woolrich et al., 2009). For stroke patients, all images were reoriented such that stroke lesions were positioned on the left side to facilitate first-level and group comparisons. Preprocessing of fMRI data included brain extraction (using BET), slice timing correction (to correct for interleaved slice acquisition), and head motion correction during which six parameters of head motion (translational x, y, z, yaw, pitch, roll) were calculated. Volumes were spatially filtered [using a full-width, half-maximum (FWHM) Gaussian kernel = 5 mm], temporally filtered, and co-registered to MNI standard space using a pediatric 1 mm MNI NIHPD atlas (Fonov et al., 2011).

First-level analysis of the task-based fMRI data was carried out using a General Linear Model (GLM), regressing head motion parameters out as factors of no interest. Task-related response activations were considered significant if they exceeded a voxel Z-score threshold of 3.1. Subsequently, a corrected cluster threshold of $p = .05$ was used to additionally mask the Z-score activation maps comparing activation level of each cluster to the cluster probability threshold using Gaussian Random Field Theory.

2.4 | Resting-state analysis of motor network

Resting-state fMRI data underwent similar pre-processing steps as task fMRI data with the exception of temporal high pass filtering of 100 s. Time courses of BOLD signal from white matter (WM) and cerebral spinal fluid (CSF) were extracted for use as nuisance regressors in the first level GLM of the resting-state fMRI analysis.

2.5 | Region of interest placement

Traditionally, two techniques have been used to establish the location of the hand region of the motor cortex for the purposes of seed-based rs-fMRI analysis: anatomical identification based on landmarks (i.e., the "omega-shaped" gyrus of the primary motor cortex; Yousry et al., 1997) and functional localization based on fMRI using a hand movement task. A previous study demonstrated there was no difference between the functional connectivity maps generated using these techniques in healthy individuals (Golestani & Goodyear, 2011). However, because of variability of perinatal stroke lesion location and volume as well as variability in post-stroke motor reorganization, anatomical localization may not be accurate for localizing the hand region of the motor cortex following perinatal stroke. Hence, localization using task-based fMRI was used in the present study for stroke patients.

The task-based fMRI activation map for an individual patient was overlaid onto the anatomical scan in order to grossly delineate M1

using the drawing tool of FSL, ensuring that only activated voxels within intact brain tissue were selected. The M1 ROI was then transformed back into the native fMRI space using FSL's FMRIB's Linear Image Registration Tool (FLIRT). The 200 most significantly activated contiguous voxels were selected using a previously validated inter-voxel cross-correlation technique (Golestani & Goodyear, 2011) based on the highest Z-scores. This was performed for right and left M1, and subsequently saved as binary ROI masks.

ROIs for the TDC group were determined anatomically using age appropriate MNI NIHPD asymmetric (natural) pediatric templates (Fonov et al., 2011) by identifying the "hand knob" area on the right and left pre-central gyrus (Yousry et al., 1997). FLIRT was used to register both ROIs to the native fMRI space of each individual TDC subject. Each ROI was trimmed to 200 contiguous voxels (around the centroid of the ROI) using an in-house script to completely encompass the hand knob area and to stay consistent with the ROI size in the stroke patient group.

This anatomical method of ROI determination was also carried out in all stroke subjects to investigate whether the ROIs produced by the two techniques were similar. To quantify this concordance, percentages of overlapping voxels between the two differently derived ROIs for each patient were calculated using the Sørensen–Dice coefficient (Dice, 1945): % Overlap = $[2N_{\text{overlap}} / (N_{\text{functional}} + N_{\text{anatomical}})] * 100$; where N_{overlap} is the number of voxels that overlap between the functional and anatomical ROIs, $N_{\text{functional}}$ is the number of voxels in the functional ROI, and $N_{\text{anatomical}}$ is the number of voxels in the anatomical ROI.

2.6 | First-level analysis

Since all patient brains were re-oriented such that lesions were positioned on the left side, the average time-course of the BOLD signal of the voxels in the left/lesioned hemisphere functionally established M1 ROI were compared with the time-course of all other voxels using a GLM. This analysis identified voxels most highly temporally correlated with left/lesioned M1, thereby inferring functional connectivity. This was repeated using right/nonlesioned M1 as the seed ROI, creating a second map that inferred functional connectivity with right/nonlesioned M1.

2.7 | Group analysis

Group analysis was performed using the raw data of the first-level analysis, producing average connectivity maps for all three participant groups. Given the variability of the patient population, the average age of all participants was calculated and the age of each participant was demeaned and entered as covariates in the group analysis. The lesion size and localization were not included in the data analysis as it is difficult to compare infarct volume between AIS and PVI given that they are calculated differently. Group average connectivity maps were calculated using a Z-score threshold of 3.7 and clusters were corrected for multiple comparisons to a p value of .05 within FSL. Subsequently, between-group contrasts were performed to examine differences in connectivity among the TDC, AIS, and PVI groups using a Z-score threshold of 2.3 (cluster threshold $p < .05$).

2.8 | Connectivity index

An M1 connectivity index (CI) was calculated for each participant as a means to determine the relative laterality (a measure of asymmetry) of functional connections with a specified ROI. CI is based on the laterality index (LI), which is commonly used to represent the hemispheric dominance of brain activity in response to a task within specific ROIs (Seghier, 2008). That is, the strength of brain activity within an ROI in one hemisphere is compared with the strength of activity in a homologous ROI in the opposite hemisphere. We calculated CI in the following manner:

$$CI = (\text{mean Z-score ROI}_1 - \text{mean Z-score ROI}_2) / (\text{mean Z-score ROI}_1 + \text{mean Z-score of ROI}_2)$$

where, ROI_1 is the ROI that was used in the first-level analysis to create the connectivity map and ROI_2 is the homologous ROI. A CI value close to 0 indicates hemispheric symmetry between the ROIs, whereas a CI value closer to -1 indicates complete asymmetry between the ROIs (i.e., homologous ROI_2 is not connected to ROI_1). Two CIs were calculated for each subject: one using Z-scores for the right/nonlesioned hemisphere M1 as ROI_1 and the left/lesioned hemisphere M1 as ROI_2 , and the other with the ROIs reversed. For healthy individuals, we anticipated that the two CIs would be similar. The CI versus infarct volume correlations for both stroke groups were also calculated.

2.9 | Motor outcomes

All stroke participants completed both the Assisting Hand Assessment (AHA) and the Melbourne Assessment of Unilateral Upper Limb Function (MA). The AHA is a validated, evidence-based hemiparetic cerebral palsy specific motor exam that tests how well a child can incorporate the paretic hand into everyday bimanual activities, whereas the MA evaluates unimanual motor capabilities of the affected arm in hemiparetic children (Cusick, Vasquez, Knowles, & Wallen, 2005; Gilmore, Sakzewski, & Boyd, 2010; Greaves, Imms, Dodd, & Krumlinde-Sundholm, 2010; Krumlinde-Sundholm, Holmefur, Kottorp, & Eliasson, 2007; Krumlinde-Sundholm, 2012). For both measures, higher scores indicate better performance with AHA expressed as logit-based scores while MA is expressed as a percentage score.

2.10 | Analysis

Initial group analysis consisted of connectivity images to estimate and describe patterns of potentially connected regions and differences between groups. To test our primary hypothesis that CI was altered in stroke subjects, a one-way analysis of covariance (ANCOVA) with age as the covariate and Tukey's post-hoc tests were used to examine differences in CI among patient groups for each ROI map separately. To test our hypothesis that bidirectional CI would be similar in TDC, a paired t -test was performed. To explore the relationship of CI to clinical function in stroke participants, motor outcome scores were compared with both sets of CI scores using a linear regression analysis with age as a covariate. Independent samples t -tests were performed to compare motor function scores between stroke groups.

3 | RESULTS

3.1 | Population

The study population consisted of 10 PVI, 10 AIS, and 20 TDC. PVI participants had a mean age of 13.5 ± 3.7 years (range 9–19 years, 5 males). AIS participants had a mean age of 14.7 ± 4.1 years (range 6–19 years, 6 males). The data from two healthy TDC were discarded due to excessive head motion (>2 mm), resulting in 18 healthy TDC with a mean age of 15.3 ± 5.1 years (7 males). There were no significant differences in demographics between groups. Motor function scores were also comparable between AIS and PVI groups for both AHA (AIS = 67.3 ± 20.4 ; PVI = 72.0 ± 14.5) and MA (AIS = 80.9 ± 21.0 ; PVI = 88.4 ± 9.7). These results are further summarized in Table 1. Lesion overlay maps illustrating lesion location and extend are demonstrated in Figure 1c.

3.2 | Congruity of ROI types

For PVI patients, the mean overlap between the functionally and anatomically derived ROIs was $64.2 \pm 4.4\%$ (range: 57.0–70.5%) in the nonlesioned hemisphere and $64.4 \pm 3.5\%$ (range: 59.0–69.0%) in the lesioned hemisphere. For the AIS patients the mean percent overlap was $26.7 \pm 15.7\%$ (range: 3.5–45.0%) in the nonlesioned hemisphere and $38.2 \pm 20.8\%$ (range: 6.5–59.5%) in the lesioned hemisphere.

3.3 | Group average connectivity maps

For all groups, the left/lesioned M1 ROI seed produced maps of significant connectivity with the contralateral right/nonlesioned M1 and supplementary motor area (SMA) (Figure 2a). In Figure 2a, in comparison to the TDC group, both the PVI and AIS groups exhibited reduced connectivity with contralateral M1 and SMA. For all groups, the right/nonlesioned M1 ROI

seed also produced maps of significant connectivity with the contralateral left/lesioned M1 and SMA (Figure 2b). Again, in comparison to TDC, Figure 2b suggests that both the PVI and AIS groups exhibit reduced connectivity with contralateral M1 and SMA. Figure 2 also suggests that connectivity is more reduced in AIS compared with PVI, for both the lesioned and nonlesioned hemispheres. The AIS group appeared to exhibit more symmetry of connections in the nonlesioned M1 seed map as compared with the lesioned M1 seed map.

3.4 | Group contrasts

Second-level group contrasts indicated that the AIS group had areas of significantly greater connectivity within the lesioned hemisphere compared with both the TDC (Figure 3a, red areas) and the PVI groups (Figure 3b, red areas) when seeded from the lesioned hemisphere M1 ROI. The localization of this greater connectivity approximated the anterior supramarginal gyrus (part of the sensorimotor association area) in the lesioned hemisphere. The AIS group also had significantly reduced connectivity compared with TDC (Figure 3a, blue areas) and PVI groups (Figure 3b, blue areas). These areas of reduced connectivity corresponded to precentral and postcentral gyri in both the lesioned and unlesioned hemispheres. Additionally, the AIS group exhibited decreased connectivity with the SMA, when compared with the TDC group.

When using the nonlesioned M1 ROI as a seed, significantly greater connectivity was again observed in the AIS group compared with both the TDC (Figure 4a, red areas) and PVI groups (Figure 4b, red areas), although the distribution appeared to be different. Increased connectivity was less prominent as compared with the lesioned M1. However, increased connectivity with the SMA was observed when AIS was compared with both TDC and PVI. Decreased connectivity in the AIS group was observed in the lesioned-hemisphere postcentral gyrus, compared with both TDC and PVI (Figure 4a,b, blue areas).

TABLE 1 Participant demographics

Demographics by participant group	AIS (N = 10)	PVI (N = 10)	TDC (N = 18)
Mean age (SD) [range] years	14.7 (4.1) [6.0–19.0]	13.5 (3.7) [9.0–19.0]	15.3 (5.1) [7.0–19.0]
Sex [%]			
Male	N = 6 [60%]	N = 5 [50%]	N = 7 [39.0%]
Female	N = 4 [40%]	N = 5 [50%]	N = 11 [61.0%]
Side of stroke (MRI) [%]			
Left	N = 7 [70%]	N = 5 [50.0%]	–
Right	N = 3 [30%]	N = 5 [50.0%]	–
Stroke volume in cc (SD)			
GM/WM lesion volume	53.6 (50.8)	–	–
Ventricle asymmetry	–	5.6 (12.0)	–
Vascular classification [%]			
Distal M1	N = 5 [50%]	–	–
Proximal M1	N = 3 [30%]	–	–
Anterior trunk	N = 1 [10%]	–	–
Posterior trunk	N = 1 [10%]	–	–
Subcortical involvement [%]			
Basal ganglia	N = 7 [70%]	N = 1 [10%]	–

AIS = arterial ischemic stroke; PVI = periventricular venous infarction; TDC = typically developing controls; SD = standard deviation; MRI = magnetic resonance imaging confirmed side of stroke; cc = cubic centimeters; ventricle asymmetry = volume of the nonlesioned ventricle subtracted from the lesioned.

FIGURE 2 Group average connectivity Z-score heat maps for three participant groups (TDC, PVI, and AIS) using either the lesioned M1 ROI (a) or the nonlesioned M1 ROI (b) as a seed. Axial images are shown in radiological convention (patient left is on the right side of the image) and are overlaid on a mean (MNI152) template in standard Montreal Neurological Institute (MNI) space. NL, nonlesioned; L, lesioned; Z, z-score; z, MNI slice level [Color figure can be viewed at wileyonlinelibrary.com]

Group comparisons between PVI and TDC showed significantly decreased connectivity with SMA for the PVI group compared with TDC, when using the nonlesioned M1 ROI seed (Figure 4c); no significant differences were observed when using the lesioned M1 ROI seed.

3.5 | CI scores

CI scores are summarized in Figure 5. For TDC participants, there was no significant difference between CI values for left and right M1 seeds. CI values for the nondominant hemisphere are illustrated in Figure 5 for simplicity with typical values between -0.17 and -0.36 (interquartile range).

CI values from the lesioned hemisphere M1 ROI differed between groups [$F(2, 34) = 5.9, p < .007$]. A post hoc Tukey test showed that CI was lower for AIS as compared with TDC ($p < .01$), as well as PVI compared with TDC ($p < .05$). AIS and PVI CI from the lesioned M1 seed did not differ from each other.

CI values from the nonlesioned hemisphere M1 ROI also differed across groups [$F(2, 34) = 4.02, p < .03$]. A post hoc Tukey test showed that AIS CI was lower as compared with TDC ($p < .05$). TDC and PVI groups did not differ ($p > .05$) nor did AIS and PVI groups ($p > .05$).

Within the PVI group, CI for the lesioned hemisphere M1 ROI was significantly lower than the nonlesioned M1 [$t(9) = -3.53, p < .006$]. There was no difference between sides within the AIS group.

CI values for both the PVI and the AIS groups were not correlated with either of the motor outcome scores (Figure 6), regardless of seed ROI.

In comparing CI values versus infarct volume correlations for the AIS children, there was a significant relationship between infarct volume and the amount of asymmetry, only when seeding from the lesioned hemisphere ($r = -0.658, p = .039$). For PVI children, there was no relationship between ventricle asymmetry and CI laterality.

4 | DISCUSSION

We have demonstrated that resting motor networks can be visualized in children with perinatal stroke and cerebral palsy. We describe disturbances in both regional and distant functional connectivity across both the lesioned and nonlesioned hemispheres. Common patterns but also specific differences may exist between arterial and venous stroke types. No powerful correlations were observed between our estimates of functional connectivity and measures of motor function

FIGURE 3 Group level contrasts illustrating significant differences in connectivity for AIS compared with TDC (a) and PVI (b) when using the lesioned hemisphere M1 ROI as a seed. Values are expressed as Z-scores where red heat maps represent higher connectivity and blue heat maps represent lower connectivity in the AIS group. NL, nonlesioned; L, lesioned [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 4 Group level contrasts illustrating significant differences in connectivity for AIS compared with TDC (a) and PVI (b) when using the nonlesioned hemisphere M1 ROI as a seed. Panel c illustrates differences between PVI and TDC. Values are expressed as Z-scores where red heat maps represent higher connectivity and blue heat maps represent lower connectivity in the AIS group. NL, nonlesioned; L, lesioned [Color figure can be viewed at wileyonlinelibrary.com]

suggesting that an additional study is required to determine clinical relevance.

The potential power of functional connectivity imaging with rs-fMRI is amplified in the developing brain. Resting motor networks have been suggested to be one of the earliest developing resting-state networks, having been successfully visualized in pre-term infants (Fransson et al., 2007), neonates (Lin et al., 2008; Liu, Flax, Guise, Sukul, & Benasich, 2008), and even in utero (Thomason et al., 2015). Evidence suggests that the “strength” of these motor networks increases with age (Lin et al., 2008; Thomason et al., 2015). Our study of perinatal stroke brings unique additional insight into developmental neuroplastic mechanisms that may evolve following early, unilateral parenchymal damage at specific times prior to or near birth before mature networks are established. In all three groups studied here (TDC, AIS, and PVI), significant cortical connections were observed between the M1 ROIs and contralateral M1 and SMA, demonstrating largely intact major motor networks on a simple scale. Similar studies of the motor network in TDC may have better demonstrated additional major nodes in the motor network such as premotor areas (Biswal et al., 1995; Ma, Narayana, Robin, Fox, & Xiong, 2011). Considering the close proximity of these areas to our M1 seeds, it is possible that we lacked the spatial resolution to discern these specifically. Such need for increasing the sensitivity and specificity of rs-fMRI approaches in pediatric populations is an evident area for future growth.

While common patterns of altered connectivity were observed, so too were specific differences between the PVI and AIS groups. In

comparison to TDC, both PVI and AIS groups showed less connectivity between the nonlesioned M1 ROI and SMA. AIS patients also showed decreased connectivity between the nonlesioned M1 ROI and secondary somatosensory areas. A decrease in functional connectivity between motor regions is often seen in other central motor diseases, suggesting that this decrease in functional connectivity between areas of the motor network can be related to the motor deficits themselves (Filippi, Agosta, Spinelli, & Rocca, 2013; Park et al., 2011; Woodward, Gaxiola-Valdez, Goodyear, & Federico, 2014). Identifying an anatomic, functionally specific region of differential connectivity such as SMA represents an exciting advance for understanding developmental plasticity after perinatal stroke.

Another example of this disease specificity was the increased connectivity seen in the lesioned M1 of AIS subjects. Adult stroke studies have shown that cortical stroke patients often have greater connectivity of the lesioned M1 within perilesional brain regions whereas those with subcortical strokes have greater alterations in interhemispheric connections (see below) (Park et al., 2011; Wang et al., 2010). Both of these adult findings are reminiscent of the alterations we observed here. However, the mechanisms of neuroplasticity that lead to such arrangements are still expected to differ between injuries acquired in fully developed versus perinatal brains. For example, even if lesioned M1 regional connectivity is higher in both adult and perinatal populations, there are surely differences in what this reflects neurophysiologically given that the adults may recruit established neighboring regions while the children have developed their motor networks around such injuries. How these mechanisms differ may provide novel insight into stroke recovery mechanisms in stroke patients of all ages.

Our results are complementary to emerging evidence from imaging and TMS studies on the importance of interhemispheric connections for motor function after perinatal stroke. In comparing the CI values across groups, the largest differences were observed between TDC and AIS, using both the lesioned and nonlesioned M1 ROI, while PVI participants demonstrated more modest alterations in interhemispheric

FIGURE 5 Comparison between mean M1 connectivity index (CI) scores across the TDC, PVI and AIS participant groups. CI scores calculated using the nonlesioned (NL) and lesioned (L) M1 ROI are represented above. A more negative CI value indicates greater asymmetry (less connectivity) between the two primary motor cortices

FIGURE 6 Connectivity indices (CIs) for lesioned M1 seed (a) and nonlesioned M1 seed (b) in relation to motor function on the Assisting Hand (AHA) and Melbourne (MA) Assessments. CI scores approaching 0 denote symmetric connectivity between motor cortices and those approaching -1 denote asymmetric connectivity. Note that CI values in panel B have been converted to negative values for comparison between panels [Color figure can be viewed at wileyonlinelibrary.com]

connectivity. Our stroke groups are immediately comparable to adult stroke subpopulations where many studies have distinguished similar large cortically based lesions from more isolated subcortical strokes. Many cortical lesions may directly compromise portions of the regions of the motor network we are attempting to evaluate with rs-fMRI. In contrast, pure subcortical lesions may leave the interhemispheric cortical networks in place and more accessible to evaluation. Such contrasts have been hypothesized to explain some of the variability in adult stroke neuromodulation trials (Lefaucheur et al., 2014). Differences in timing of injury—PVI prior to 34 weeks and AIS near term—may bring additional complexity in the perinatal stroke population. A final consideration regarding assessment of interhemispheric interactions is that our rs-fMRI estimates of altered connectivity are not able to imply directionality or relative balance of excitation versus inhibition. New TMS data in the same population shows that many children with perinatal stroke have interhemispheric facilitation (in contrast to normal inhibition), the degree of which is positively associated with clinical function (Eng et al., 2017). Caution is clearly required in interpreting any of these modalities with careful respect of what they can, and cannot, demonstrate.

In both stroke groups, no significant relationship was observed between CI scores and AHA or MA scores. This finding was not entirely surprising as our study was powered to show imaging patterns and not clinical associations which are known to be highly variable in this population. Even simple imaging biomarkers such as lesion volume and location are only modestly reliable in predicting outcomes and usually only on a very general level (e.g., hemiparesis or not) (Boardman et al., 2005; Lee et al., 2005). Additional considerations include the limited ability of the AHA and MA to measure real world clinical function. However, in adult stroke, laterality indices have been correlated with motor outcome scores though usually with larger samples. To address whether this was simply a statistical power issue, if we combined our entire sample of 20 stroke subjects and regressed AHA scores against CI based on observed CI standard deviation of 0.13, standard deviation of the regression errors of 2.6, and type I error of 0.05, our power increased to 88% to show an estimated

significant slope of 15. These results suggest we were likely underpowered to detect this level of correlation between outcome and CI when separating out patients by stroke groups. There are almost certainly additional complexities mediating the relationship between network assessments and clinical function to be considered.

Our findings open the door for further studies of functional connectivity after perinatal stroke. Investigating the wider sensorimotor network by including primary sensory, premotor, and supplementary motor cortices may be more informative than restricting models to just primary motor cortex. Additional recruitment of more remote areas that are part of the sensorimotor network may also be of interest such as posterior parietal cortices. Recent robotic studies have demonstrated the common occurrence of sensory dysfunction in children with perinatal stroke and its effect on clinical function (Kuczynski, Dukelow, Semrau, & Kirton, 2016; Kuczynski, Semrau, Kirton, & Dukelow, 2017). While motor organization often involves the contralesional hemisphere, sensory pathways are almost always maintained to the contralateral hemisphere (Staudt, 2007). This has been hypothesized to create a “disconnect” between sensory and motor areas that may impact function but also be amenable to interrogation with rs-fMRI.

Further, the role of subcortical (thalamus, caudate) and cerebellar areas could also be examined to more fully encompass the larger motor network. We were surprised to find that our M1 ROIs did not show consistent connections to subcortical motor regions such as the thalamus, caudate, lentiform nucleus or cerebellum as expected from adult studies (Carter et al., 2010). It is possible that the size of these subcortical regions were too small in our pediatric sample to survive the multiple comparison correction applied to clusters of brain activity.

Resting-state fMRI promises to be a beneficial tool for use in populations that are unable to perform tasks during MRI. In children with cerebral palsy, often even the simplest tapping task is very difficult in light of significant hemiparesis. Indeed, in our study the more severely paretic participants had to sometimes use their full arm, shoulder, and torso in order to press the button during the task,

resulting in head motion. In addition, level of difficulty is confounded between and within patient groups, further adding variability to activation patterns across the group. Using resting-state fMRI effectively removes, or at least reduces, these two types of confounds by avoiding the need for task. Demonstrating that motor networks can be measured at rest in young children with hemiparesis is a major step forward in examining motor network plasticity in perinatal stroke.

Future resting state studies could investigate effective connectivity via a regression model thus more specifically capturing modulations in excitatory and inhibitory connectivity among motor regions. This is something that could not be explored in the current study given the nondirectional correlation analysis performed. Investigations could also be expanded to explore connectivity within (integration) and between (segmentation) larger networks via the functional connectome and graph theory metrics though would be challenging given the heterogeneity of lesions. These studies may shed light on patterns of re-organization after perinatal stroke, especially the excitatory-inhibitory balance between hemispheres that is no doubt disrupted and may result in motor dysfunction (Staudt, 2010). TMS neurophysiology is an additional invaluable tool to provide converging evidence regarding re-organization, inhibitory interhemispheric processes and further noninvasive brain stimulation treatment avenues.

Several challenges and limitations are identified. Younger participants, particularly those under the age of 10 years, often have difficulty lying still for the entire imaging session. This applied to both healthy TDC and the stroke participants and may have biased our sample to older and less impaired participants. Two TDC participants had to be excluded for motion. Advances in pediatric imaging practices and post hoc head motion correction algorithms may mitigate these in the future. Another large challenge was the variability in size and location of stroke lesions in the AIS group. Pre-processing steps were carefully monitored to ensure that registration was properly carried out so that the large cortical lesions did not introduce errors to the resulting connectivity maps. It remains possible that variability in lesion locations contributed to the overall variability in connectivity scores, especially since it was challenging to factor in dependent variables such as the size and localization of the lesion into the group assessment as covariates. While this is a challenge for group statistics, the variability in lesion locations and size are representative of the wider AIS population. Our sample size was modest, limiting our power to demonstrate differences across complex outcomes and groups while increasing the risk of chance associations. We note that the only other rs-fMRI perinatal stroke study was able to observe correlations between connectivity and complex clinical outcomes with a sample of similar size. It is also important to consider that while evidence has suggested that PVIs occur in utero and present as presumed perinatal ischemic stroke, the pathophysiological mechanism of this type of injury does differ from perinatal arterial ischemic strokes and it could be argued that PVI are not considered "true" strokes. However, given that the injury occurs in the perinatal period and results in hemiparetic cerebral palsy, we feel that the comparison between the two groups is appropriate. Our sample was also necessarily composed of slightly higher functioning perinatal stroke children due to the finger-tapping task used to localize M1. Since children with more severe hemiparesis (i.e., MACS level 5), are often unable to complete motor tasks without

excessive head motion, the sample was biased to less-severely impaired children. Our study will hopefully facilitate recruitment of larger samples capable of confirming or modifying our results while advancing the application of this powerful imaging tool to address deeper questions in children with cerebral palsy.

Our results provide preliminary evidence in support of the feasibility of visualizing the strength of functional connections within the motor network in a perinatal stroke population. Differences in connectivity relative to healthy TDC are evident, informing models of developmental plastic motor organization that might be targeted with therapeutic interventions such as noninvasive brain stimulation.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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