Sensory-motor network functional connectivity in children with unilateral cerebral palsy secondary to perinatal stroke

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ABSTRACT

Background: Perinatal stroke is the most common cause of unilateral cerebral palsy. Mechanisms of post-stroke developmental plasticity in children are poorly understood. To better understand the relationship between functional connectivity and disability, we used resting-state fMRI to compare sensorimotor connectivity with clinical dysfunction.

Methods: School-aged children with periventricular venous infarction (PVI) and unilateral cerebral palsy were compared to controls. Resting-state BOLD signal was acquired on 3 T MRI and analyzed using CONN in SPM12. Functional connectivity was computed between S1, M1, supplementary motor area (SMA), and thalamus of the left/non-lesioned and right/lesioned hemisphere. Primary outcome was connectivity expressed as a Fisher-transformed correlation coefficient. Motor function was measured using the Assisting Hand Assessment (AHA), and Melbourne Assessment (MA). Proprioceptive function was measured using a robotic position matching task (VarXY).

Results: Participants included 15 PVI and 21 controls. AHA and MA in stroke patients were negatively correlated with connectivity (increased connectivity = poorer performance). Position sense was inversely correlated with connectivity (increased connectivity = improved performance) between the non-lesioned S1 and thalamus/SMA. In controls, VarXY was positively correlated with connectivity between the thalamus and bilateral sensorimotor regions.

Conclusions: Resting state fMRI measures of sensorimotor connectivity are associated with clinical sensorimotor function in children with unilateral cerebral palsy secondary to PVI. Greater insight into understanding reorganization of brain networks following perinatal stroke may facilitate personalized rehabilitation.

1. Introduction

Perinatal stroke is a focal vascular injury that occurs in the developing brain between 20 weeks of gestation and the 28th postnatal day (Nelson, 2007). It occurs in at least 1:2500 live births, affecting up to 10,000 Canadian children (Raju et al., 2007). Morbidities among survivors include gross and fine motor difficulties, language problems, behavioural abnormalities, and epilepsy (Golomb et al., 2001; Sreenan et al., 2000; Mercuri et al., 2004; Lee et al., 2005; deVeber et al., 2000). Perinatal stroke is the most common cause of unilateral cerebral palsy where damage to major components of the motor system results in contralateral weakness and lifelong physical disability (Nelson, 2007;

Nelson, 2003; Nelson and Lynch, 2004). Periventricular venous infarction (PVI) is a stroke subtype that can often selectively injure the descending corticospinal tracts (and additional periventricular white matter) while sparing the overlying motor cortex. Such focal injury of defined timing in an otherwise healthy brain makes perinatal stroke an ideal human model of developmental neuroplasticity (Kirton, 2013).

Post-stroke plasticity has been well studied in adult stroke patients (Plow et al., 2015; Starkey and Schwab, 2014; Bütefisch, 2004), but mechanisms of plasticity and implications for rehabilitation in children likely differ and are poorly understood. Most plasticity studies in adult stroke and cerebral palsy have focused on the motor system. Though evolving models differ based on multiple factors including age and

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lesion, common themes include recruitment of contralateral, non-lesioned motor areas including primary motor cortex and related network components such as supplementary and premotor cortices (Bütefisch, 2004; Jiang et al., 2013).

Perinatal stroke also injures the sensory network, yet disordered sensory function and its contribution to disability has been relatively ignored in cerebral palsy. Previous studies suggest that sensory deficits in perinatal stroke may relate to decreased functional connectivity in the lesioned somatosensory network (Dinomais et al., 2012), which likely exacerbates poor motor functioning. Crude measures of sensory function have been used to date, but modern robotic technologies have enhanced our understanding of sensorimotor dysfunction. Specifically, proprioception can be assessed quantitatively to provide more accurate measurements. We recently used robotic technology to define the common occurrence of disordered position sense (Kuczynski et al. 2016) and kinesthesia (Kuczynski et al., 2017a) in children with perinatal stroke and its contribution to clinical disability. We have also linked this dysfunction to disordered structural connectivity of sensory pathways using diffusion tensor imaging (Kuczynski et al., 2017b).

A major outstanding gap in knowledge is understanding how integrated sensorimotor networks develop following perinatal stroke. The advanced MR imaging that has helped define the above models has progressed to include resting-state functional MRI. This has afforded new opportunities to explore functional connectivity and its alterations across the motor network following stroke in adults, however applications in the developing brain have been limited (Thiel and Vahdat, 2015). A recent controlled resting state fMRI study of children with perinatal stroke suggested differences in default mode network connectivity in arterial but not venous lesions (Ilves et al., 2016). Improving such models can define central therapeutic targets for neuromodulation with immediate translational significance as evidenced by recent positive controlled trials of non-invasive brain stimulation in this population (Kirton et al., 2016; Kirton et al., 2017).

Combined sensorimotor functional connectivity has not been extensively described in children with unilateral cerebral palsy secondary to perinatal stroke. To better understand the relationship between sensorimotor functional connectivity and clinical disability, we completed a controlled study using resting-state fMRI and the best available measures of motor and sensory dysfunction in children with perinatal stroke. We hypothesized that decreased sensorimotor connectivity of the lesioned hemisphere would correlate with measures of clinical disability.

2. Methods

2.1. Participants

Participants were recruited via a population-based research cohort (Alberta Perinatal Stroke Project) (Cole et al., 2017) and the Healthy Infants and Children Clinical Research Program (www.hiccupkids.ca) at the Alberta Children's Hospital. PVI diagnosis was confirmed with clinical neuroimaging reviewed by two experts and classified according to established criteria (Kirton et al., 2008). PVI participants were between 6 and 19 years of age, had symptomatic unilateral cerebral palsy as determined by a Manual Ability Classification System score of I-IV and perceived disability by child and parent, (Eliasson et al., 2006) born at > 36 weeks gestation, and no history of other neurological conditions. Typically developing (TD) controls were right-handed, between the ages of 6 and 19 years and had no neurological conditions, medications, or MRI contraindications. TD participants were recruited to balance gender and age with stroke cases. Prior to participation, informed written parental consent and participant assent where appropriate were obtained. This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

2.2. Sensorimotor function

Clinical sensorimotor function was measured using a bilateral exoskeleton robot (KINARM) in an augmented reality environment (Kuczynski et al., 2016; Dukelow et al., 2010; Dukelow et al., 2012). In the position matching task, the robot moved the affected limb up to 8 different spatial locations and the blindfolded participant was required to match each position with their unaffected arm. Spatial variability (in cm) from the expected limb position in the XY plane (VarXY) was the primary sensory outcome. Higher values of VarXY indicated poorer position matching performance.

Motor function was assessed for the stroke group by trained, certified physical (PT) or occupational therapists (OT). Two validated motor function tasks for children with unilateral cerebral palsy were used; the Assisting Hand Assessment (AHA), and the Melbourne Assessment of Unilateral Upper Limb Function (MA). All sessions were video-taped and scored offline. The AHA is a 22-item assessment tool that measures spontaneous bimanual hand function in children with motor impairments (Holmefur et al., 2007; Krumlinde-Sundholm et al., 2007; Krumlinde-sundholm and Eliasson, 2003). It has the advantage of using real-world activities to measure spontaneous bimanual motor function rather than testing the affected hand in isolation. The primary motor outcome was the AHA score in logit units ranging from 22 (hand is not used at all) to 88 (normal motor function). The MA consists of 16 tasks that measure motor function in unilateral upper limbs (Bourke-Taylor, 2003; Randall et al., 1999). Typical tasks include reaching and grasping different sized objects, reflecting finger dexterity and speed of motion. Raw scores ranging from 0 (no achievement) to 122 points (no impairment) were subsequently converted to percentages [MA% = (# of points achieved/total # points possible) * 100].

2.3. Imaging

MRI sequences were acquired using a standardized perinatal stroke neuroplasticity protocol at the Alberta Children's Hospital Diagnostic Imaging Suite using a dedicated research 3.0 Tesla GE MR750w MRI scanner (GE Healthcare, Waukesha, WI) with an MR Instruments 32-channel receive-only head coil. High-resolution anatomical T1-weighted fast spoiled gradient echo (FSPGR BRAVO) images were acquired in the axial plane [166 slices, no skip; voxel size = 1.0 mm isotropic; repetition time (TR) = 8.5 ms; echo time (TE) = 3.2 ms; flip angle = 11°; matrix = 256 × 256].

Resting-state fMRI acquisition used 150 T2-weighted whole brain echo planar volumes (EPI; 36 interleaved contiguous slices; voxel size = 3.6 mm isotropic; TR = 2000 ms; TE = 30 ms; flip angle = 60°; matrix = 64 × 64). Five volumes (10 s) were discarded at the beginning of each functional run to attain magnetic field equilibrium. Participants were told to fixate on a centrally presented cross. Since the location of PVI could occur in either hemisphere, images were reoriented such that the stroke was located in the right hemisphere for all patients. Therefore, hemispheres are referred to as lesioned vs intact in PVI patients rather than right vs left (as in TD controls).

Resting-state functional connectivity analyses were performed using the SPM12 (Statistical Parametric Mapping, Wellcome Trust, UCL, UK) Functional Connectivity Toolbox (CONN) (Whitfield-Gabrieli and Nieto-Castanon, 2012). Slice timing correction, realignment, and co-registration were performed, and head motion parameters were estimated. Co-registered images were segmented using standard SPM tissue probability maps. Images were normalized into Montreal Neurological Institute (MNI) space via direct non-linear transformations using the standard 152-average template. Direct normalization results in structural and functional volumes being separately normalized to MNI space. Images were then smoothed with a 6 mm³ full-width at half-maximum (FWHM) Gaussian kernel. Head motion and other outliers were identified using the Artifact Repair Toolbox (Mazaika et al., 2007) by detecting volumes with global mean signal change greater than z = ± 9
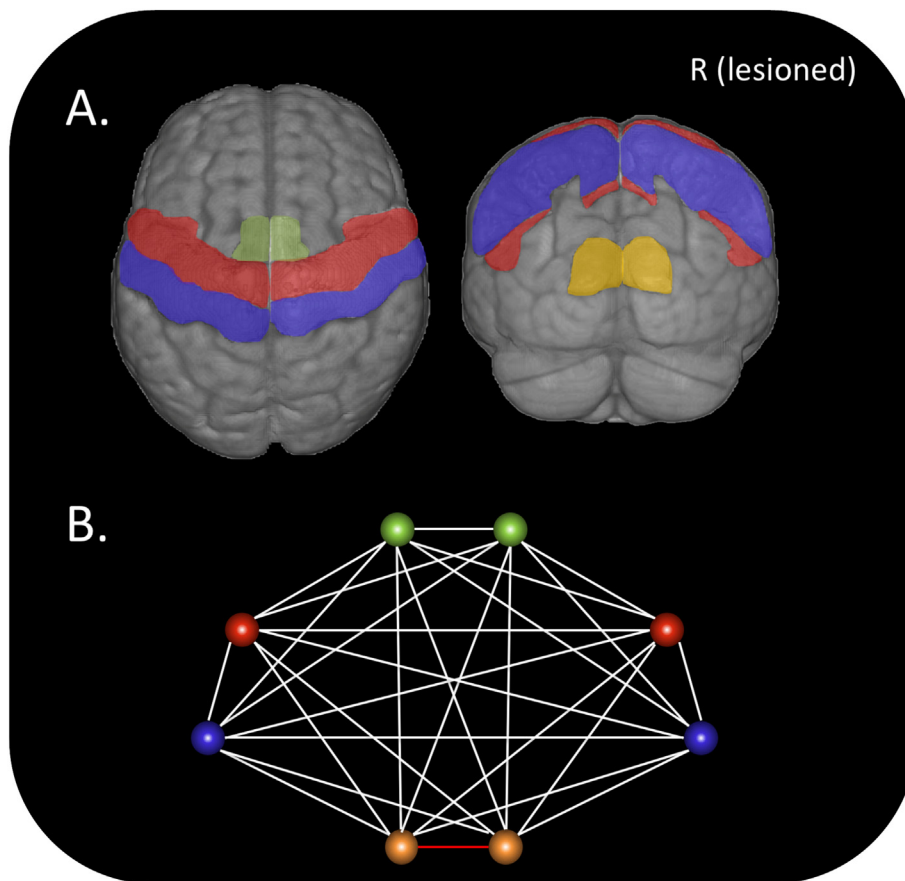
Fig. 1. A. Anatomic representation of nodes used for resting-state correlation (red = M1, blue = S1, green = SMA, orange = thalamus). B. Differences between PVI and controls in resting-state connectivity between nodes (calculated using a series of unpaired *t*-tests comparing Fisher transformed correlation coefficients between both groups), whereby control subjects had significantly greater connectivity between bilateral thalami, shown using red line (*p*-value = .018, corrected using Holm-Bonferroni for multiple comparisons). Right/lesioned hemisphere indicated on figure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

or exceeding 2 mm of head movement. Time courses of blood oxygenation level dependent (BOLD) response were extracted for the GM, CSF and WM. The CSF and WM time courses were regressed out of the general linear regression model (GLM). Outlier volumes and head motion (as identified by ART) were de-weighted in the GLM.

Subsequent ROI-to-ROI connectivity analyses were performed using four predetermined seeds of interest selected via the FSL Harvard-Oxford Atlas: left and right primary motor cortices (precentral gyri: LM1 = 35.27 cm^3 in size (cc), RM1 = 24.28 cc), left and right primary somatosensory cortices (postcentral gyri: LS1 = 29.3 cc, RS1 = 25.91 cc), left and right supplementary motor areas (LSMA = 5.46 cc, RSMA = 5.98 cc), and left and right thalamus (LThal = 10.24 cc, RThal = 10.78 cc) (Desikan et al., 2006) (Fig. 1 A). A fifth control ROI removed from the motor network was also examined as a non-motor region for comparison (non-lesioned anterior temporal pole: LTP = 18.86 cc). Time-series were calculated using the average of all voxels within the ROI. Fisher-transformed correlation coefficients were calculated between each of the ROIs and interpreted as quantifications of connectivity strength between nodes.

2.4. Statistical analyses

The Statistical Package for the Social Sciences (IBM SPSS Version 19 for Windows, Chicago, USA) was used for statistical analyses. Data was checked for normality using the Shapiro-Wilks test. Normally distributed group means were compared using Student *t*-tests. Translational and rotational head motion was compared between groups using independent samples Mann-Whitney *U* tests. Pearson correlation coefficients were calculated to quantify between-node connectivity strength, age, gender, and sensorimotor function (VarXY, AHS wood MA). The Holm-Bonferroni method was used to correct for multiple comparisons (Holm, 1979).

3. Results

3.1. Population

Thirty-eight participants were studied: 17 PVI (median age 11.3 years, interquartile range 9.1–14.5, 64.7% male) and 21 controls (median age 12.6 years, interquartile range 9.5–15.5, 52.3% male). Of the PVI patients, 9 had lesions in their left hemisphere. Two PVI participants were excluded due to motion artifact. Robotic sensory data was available for 14 PVI subjects. Complete motor (MA) and sensory (AHA) outcomes were available for 14 PVI subjects. VarXY measurements were available for 17 controls. VarXY scores for controls (mean distance 3.55 ± 1.02) were better than PVI subjects (mean distance 5.58 ± 1.89), in that they were closer to the target when moving their hand in space (*p* = .001). There were no significant correlations between age or gender and the imaging or sensorimotor outcomes. Full details on participant demographics and performance scores are available in Table 1.

3.2. Resting-state networks

Resting-state networks were measurable in all subjects. Strong, symmetrical inter-hemispheric connections for M1-M1 and S1-S1 connectivity were observed in both controls (M1-M1: 1.172 ± 0.22, S1-S1: 1.229 ± 0.26), and PVI patients (M1-M1: 1.002 ± 0.31, S1-S1: 1.116 ± 0.36). Intra-hemispheric connections between each M1-S1 were symmetrical and strong but lower in comparison to interhemispheric values for both controls (RM1-S1: 1.106 ± 0.33, LM1-S1: 0.972 ± 0.32) and PVI patients (lesioned RM1-S1: 0.955 ± 0.33, non-lesioned LM1-S1: 0.849 ± 0.31). There were significant differences between controls (1.103 ± 0.284) and PVI (0.807 ± 0.369) cases when comparing the left thalamus to the right thalamus, with the controls

Table 1

Patient and control demographics. N/a = data not available as patient did not or was unable to perform task. The bottom row is a summary and lists median age with the interquartile ranges listed in brackets, and average performance scores with standard deviation.

Group	Age at Scan	Gender	Lesioned hemisphere	MA score	VarXY	AHA score
PVI	17.5	M	L (posterior frontal)	79.78	6.604	60
PVI	19.6	F	R (frontal)	100	6.232	100
PVI	14.5	F	L (frontal)	91.01	3.151	73
PVI	13.1	F	R (internal capsule)	74.16	n/a	57
PVI	11.3	M	L (frontoparietal)	95.51	6.145	84
PVI	9.7	F	L (frontal)	97.75	4.208	83
PVI	13.1	M	L (frontal)	98.88	4.771	81
PVI (excluded)	8.4	M	R (frontal)	96.63	9.077	100
PVI	9.1	F	R (frontal)	85.39	3.761	60
PVI	8.6	M	L (frontal)	88.76	n/a	62
PVI	11.4	M	R (frontal)	86.52	6.159	62
PVI	19.7	M	R (frontoparietal)	75.28	8.512	60
PVI	10.6	M	L (internal capsule)	n/a	4.046	n/a
PVI	11.0	M	R (frontal)	66.29	3.472	55
PVI (excluded)	6.6	M	R (frontal)	95.51	n/a	87
PVI	16.2	M	L (frontoparietal)	n/a	7.538	n/a
PVI	6.9	F	L (frontopatietal)	n/a	4.421	n/a
	11.3 (9.1–14.5)	11 M	9 L	87.96 ± 10.58	5.58 ± 1.89	73.14 ± 15.85
Control	13.2	M	n/a	n/a	n/a	n/a
Control	9.4	M	n/a	n/a	5.956	n/a
Control	18.5	F	n/a	n/a	n/a	n/a
Control	11.8	M	n/a	n/a	5.260	n/a
Control	9.2	M	n/a	n/a	n/a	n/a
Control	9.8	M	n/a	n/a	4.217	n/a
Control	16.4	M	n/a	n/a	3.919	n/a
Control	6.6	M	n/a	n/a	3.062	n/a
Control	9	F	n/a	n/a	3.926	n/a
Control	13.2	F	n/a	n/a	2.841	n/a
Control	9.5	F	n/a	n/a	2.887	n/a
Control	12.6	F	n/a	n/a	2.621	n/a
Control	18.3	F	n/a	n/a	3.348	n/a
Control	13.7	F	n/a	n/a	n/a	n/a
Control	15.5	M	n/a	n/a	4.003	n/a
Control	19	F	n/a	n/a	2.582	n/a
Control	11.6	F	n/a	n/a	2.574	n/a
Control	8.2	M	n/a	n/a	2.954	n/a
Control	10.4	M	n/a	n/a	2.976	n/a
Control	12.8	M	n/a	n/a	4.664	n/a
Control	16.3	F	n/a	n/a	2.509	n/a
	12.6 (9.5–15.5)	11 M			3.55 ± 1.02	

having greater connectivity ($p = .010$) (Fig. 1 B). Correlation coefficients between sensorimotor nodes and the control temporal lobe region were generally low (Fisher score < 0.3) (Supplementary Table 1). Neither translational nor rotational head motion was different between PVI and TDC.

3.3. Correlations with task performance

AHA scores in stroke participants were negatively correlated with resting-state values between multiple nodes, such that increased connectivity was associated with poorer performance. Connectivity between M1 of the non-lesioned hemisphere to the ipsilateral SMA was associated with motor function as assessed with the AHA (Fig. 2 A). All correlations between node connectivity estimates and Melbourne (MA) scores in stroke participants were nonsignificant (Fig. 2 B).

For robotic sensory measures, VarXY scores in stroke participants were correlated with resting-state values between multiple nodes such that increased connectivity was associated with better performance (lower VarXY). Associations were related to the non-lesioned S1 and its connections to bilateral thalami (ipsilateral thalami $r = -0.630$, $p = .015$; contralateral thalami $r = -0.623$, $p = .0017$) and contralateral SMA ($r = -0.624$, $p = .017$) (Fig. 2C). In contrast, VarXY scores in controls were positively correlated with resting-state values, such that increased connectivity was associated with poorer performance, with significant correlations relating to bilateral thalami and sensorimotor nodes (Fig. 2 D) (see Supplementary Table 2 for values).

4. Discussion

Our study supports the feasibility of measuring resting-state sensorimotor networks in children with unilateral cerebral palsy secondary to perinatal stroke. We demonstrated the ability to isolate relevant primary and secondary motor and sensory nodes and estimate their relative functional connectivity. Correlations observed between specific node connectivity and validated functional measures support clinical relevance. These findings suggest resting state fMRI is an important addition to emerging imaging tools that can be used to better understand the developmental plasticity of neural networks following early brain injury.

The motor network is one of the most extensively studied resting-state networks, both in the healthy brain and across disease states. Less often, motor and sensory cortices are considered together because of their integrated functional roles and anatomical locations. In this study, we were able to separate these locations in both controls and PVI subjects to make some general estimates of overall functional connectivity. Both controls and stroke patients demonstrated stronger interhemispheric connections between M1-M1 and S1-S1, than intra-hemispheric connections between M1-S1. This is consistent with expected relationships and reassuring that our method of separating M1 nodes from S1 nodes was not confounded by a significant amount of overlap (where artificially stronger intra-hemispheric M1-S1 connectivity would be expected). The large degree of similarity compared to controls also suggests that PVI patients have relatively intact
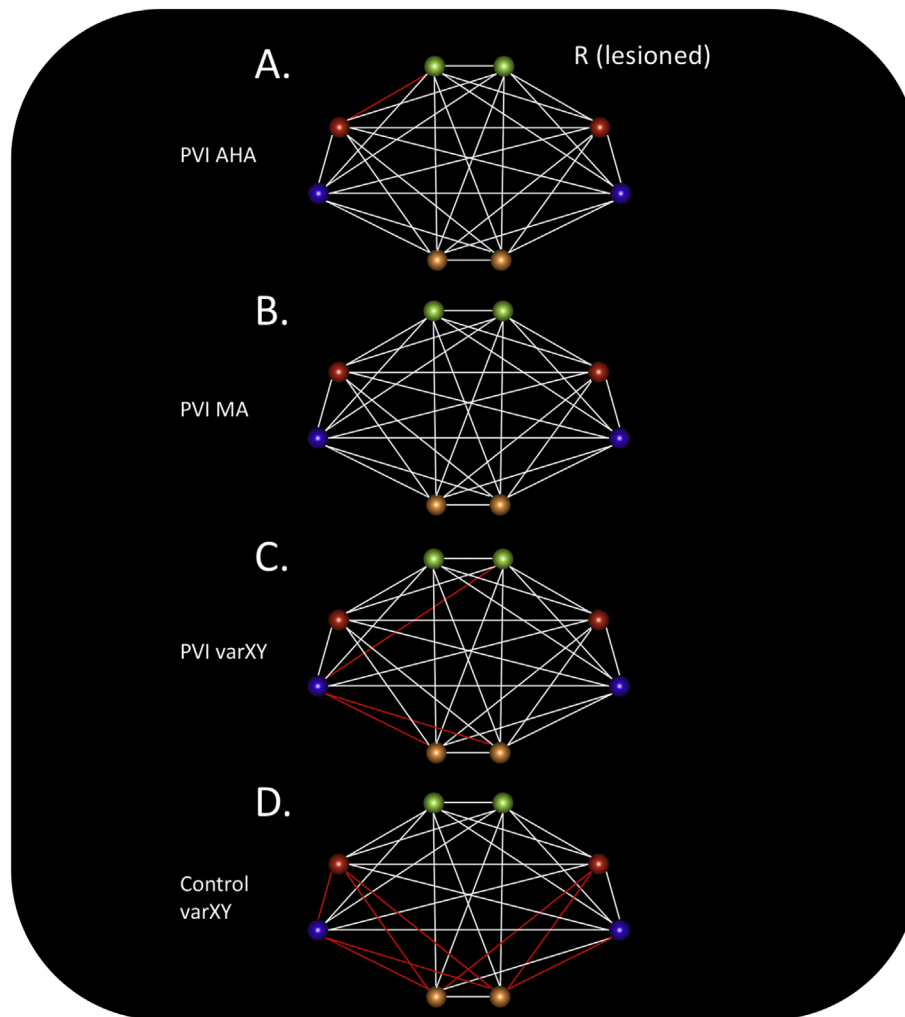
Fig. 2. Pearson's correlations between resting-state connectivity and performance in various tasks. Significant correlations are shown using red lines (*p*-value < .05, corrected using Holm-Bonferroni (please see specific *p*-values and HB corrected p-values in Supplementary Table 2). Correlation between PVI subjects' connectivity and A. AHA performance, B. MA performance, and C. VarXY performance. D. Connectivity between control subjects' connectivity and VarXY performance. Right/lesioned hemisphere indicated on figure. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

networks (Supplementary Table 1). Strong M1-M1 correlations similar to our findings have been demonstrated using various neuroimaging techniques in adult stroke patients (Xu et al., 2014; Bütefisch et al., 2008; Rehme et al., 2011), reaffirming the importance of these interhemispheric connections in motor function and motor recovery. Such an ability to explore specific connections brings a new power to the understanding of developmental plastic organization following early brain injury. Preliminary studies have suggested that sensory pathways almost always remain contralateral while motor organization often moves to the ipsilateral, contralesional hemisphere. The resulting 'disconnect' between each M1 and S1 that would normally speak to each other within the same hemisphere has been hypothesized to contribute to disability (Dinomais et al., 2012). While our study does not prove this, it supports the feasibility of asking such complex connectivity questions in future studies.

That the overall cortical sensorimotor network is relatively intact in PVI subjects is further supported by the lack of significant differences we observed in connectivity between patients and controls, apart from the thalamus. PVI was deliberately chosen as the optimal perinatal stroke disease state model for this study due to it often being a relatively simple, unilateral, subcortical lesion with spared cortex by definition (Kirton et al., 2008). However, PVI can also produce a precise lesion to the motor and possibly sensory pathways in the periventricular white matter. We note that correlation coefficients were very

frequently lower in the stroke group versus controls for all connections studied, a result unlikely to be due to chance, even though the group means did not differ statistically (Supplementary Table 1). This may also reflect the relatively modest power in our sample where variance in connectivity indices was substantial. These factors will need to be considered as resting state connectivity imaging is applied to larger perinatal stroke populations, most notably arterial strokes that are even more common and typically include more complex lesions that combine cortical and subcortical injuries (Kirton et al., 2008; Kirton et al., 2011).

The thalamus showed decreased connectivity in PVI patients compared to controls, suggesting significant disruption within a main relay centre in the brain (Fig. 1). The early nature of PVI lesions has previously been suggested as a reason why sensory pathways may be successful in "re-routing" to maintain their connections to the contralateral sensory cortex (Staudt, 2007). However, our new observations here may suggest that such early lesions can also disrupt development of larger sensory network components. We have also recently observed that increased contralesional thalamic volume is associated with greater disability in children with perinatal stroke (Craig et al., under revision), further suggesting that deeper explorations of the entire sensorimotor network are required.

Connectivity strength was correlated with motor and sensory performance scores. That such differences were focused around the contralesional M1 and S1 for motor (AHA, Fig. 2A) and sensory (varXY,

Fig. 2C) outcomes respectively supports their clinical relevance. These findings are also consistent with the established importance of the contralesional hemisphere in both animal (Martin et al., 2011) and human (Kirton, 2013; Staudt, 2007; Eyre, 2007) models of sensorimotor developmental plasticity following early unilateral brain injury. As the physiology of these key contralesional nodes is further defined by other imaging and brain stimulation modalities (Zewdie et al., 2016; Carlson et al., 2017), integration with evidence from the connectivity approach utilized here may be particularly valuable. That the same locations associated with robotic sensory measures was observed in both cases and controls (contralesional S1 to bilateral thalami), and that this correlation reversed directions between the two groups, further supports the functional relevance of our findings. In addition, robotic sensory measures in controls showed correlation to bilateral primary sensorimotor node connectivity. By contrast, in PVI patients, only the contralesional primary sensory node was involved, with no significant connectivity-function relationship seen for the ipsilesional primary sensorimotor nodes (Fig. 2C and D). Stronger sensory associations were observed between thalamic nodes as compared to primary sensory cortex. In addition, these associations were positive in PVI patients (worse performance = less connectivity), but negative in control subjects (worse performance = greater connectivity). Studies comparing patients with mild TBI to controls have shown similar results, with increased thalamic network connectivity in patients compared to controls (Tang et al., 2011). One hypothesis from such studies is that thalamic GABAergic outputs normally result in relatively less network connectivity, but following disruption there may be relative disinhibition of surrounding regions and thereby increased connectivity. This may also be consistent with our observation that control subjects had poorer performance with greater bilateral thalamic connectivity. Alternatively, patients performed better with increased contralesional connectivity, possibly as a compensatory mechanism.

Adult stroke studies have suggested that stroke induced brain reorganization results in significant alterations in interhemispheric connectivity between primary sensorimotor areas (Grefkes et al., 2008). Furthermore, such reorganization has been suggested to contribute to poorer motor recovery and performance (Wang et al., 2010). Current hypotheses for subcortical adult stroke, which have marked anatomical similarities to PVI including sparing of the overlying cortex, suggest such alterations in transcallosal inhibition between the two M1, whereby the non-lesioned hemisphere exerts undue inhibitory drive on the lesioned M1, contribute to lower function (Murase et al., 2004). This model is translationally significant, driving much of the non-invasive neuromodulation trials in adults (Hsu et al., 2012). We have described abnormal interhemispheric interactions in children with perinatal stroke using transcranial magnetic stimulation (TMS) (Eng et al., 2017). While analogous models have been proposed in perinatal stroke (Gillick et al., 2014), it is also quite certain that there are expected to be marked differences in sensorimotor organization in this population. For example, we have recently described abnormal interhemispheric interactions in children with perinatal stroke using TMS where distinctly different patterns of interaction are observed (Eng et al., 2017). That contralesional M1 connectivity to secondary sensorimotor regions was associated with poorer AHA task performance may also be consistent with such a model (Fig. 2A).

Interestingly, similar studies have looked at functional connectivity in infants with perinatal brain injury. These studies demonstrate that connectivity is altered at a very early stage in development, close in time to the initial injury (Arichi et al., 2014; Linke et al., 2018; Smyser et al., 2013). This suggests that connectivity networks are altered initially, changing the developmental trajectory, then likely continue to change with external environmental influences such as rehabilitation. Specifically, studies suggest that initially the function of overlying cortex remains intact, yet thalamo-cortical tracts develop compensatory trajectories (Arichi et al., 2014). This is interesting in that our major findings were between cortical regions and the thalamus, suggesting that these pathways continue to be altered throughout development (Arichi et al., 2014). More so, connectivity changes at term-equivalent age in somatomotor cortex was shown to predict motor function at 4 and 8 months (Linke et al., 2018). This poses the question of the predictive value of connectivity measures at older ages, such as the population studied in this article, and how the connectivity changes over time with development and rehabilitation.

While finding significant correlations between the bimanual motor score, AHA, and resting-state connectivity, no such correlations were seen with the unimanual motor task, MA. The explanation underlying this result is unclear but may relate to known differences in cortical mechanisms of motor control for unimanual versus bimanual tasks. In general, the AHA and MA are both relatively crude and artificial scoring systems while the robotic proprioceptive measures may be considerably more sensitive. Applying such tools to explore motor function may represent a positive direction in this population where recent studies have linked performance and abnormalities in detailed motor skills such as visually guided reaching with imaging markers of structural connectivity (Kuczynski et al., 2017b). Further studies using such sensitive motor measures would be beneficial in better understanding motor network connectivity.

Important limitations are considered. Unfortunately, due to removal of patient data from head motion while scanning, group numbers varied between controls and patients, as well as VarXY, MA, and AHA. Despite this, there was no effect on task performance or resting state values due to age or gender in either group or between groups. We limited our study to include only those children born at term (> 36 weeks) thus reducing the possibility of damage to white matter due to premature delivery. The possibility of additional, more wide-spread white matter microstructural changes that may have affected functional connectivity cannot be entirely excluded. Further studies examining white matter in detail may be informative in this regard. In addition, patients likely received different types and amounts of therapy which could have impacted their imaging outcomes though no correlation was observed between age and our connectivity measures. Unfortunately, we do not have access to lifetime therapy hours to account for this potential confounder. The MA and AHA are also relatively artificial measures of motor function with variability in performance, observation, and scoring that must be considered in how they relate to real world function of individual children.

In conclusion, we provide novel data suggesting that resting state fMRI can assess sensorimotor functional connectivity in children with unilateral cerebral palsy secondary to perinatal stroke. That both location- and direction-specific relationships are observed between such connectivity and validated measures of disability supports clinical relevance. Such improved insight of brain network development may define imaging biomarkers to predict and understand response to emerging therapies such as neuromodulation to advance personalized rehabilitation for disabled children.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101670.

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