



Thalamic diaschisis following perinatal stroke is associated with clinical disability



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ABSTRACT

Background: Perinatal stroke causes most hemiparetic cerebral palsy and leads to lifelong disability. Understanding developmental neuroplasticity following early stroke is increasingly translated into novel therapies. Diaschisis refers to alterations brain structures remote from, but connected to, stroke lesions. Ipsilesional thalamic diaschisis has been described following adult stroke but has not been investigated in perinatal stroke. We hypothesized that thalamic diaschisis occurs in perinatal stroke and its degree would be inversely correlated with clinical motor function.

Methods: Population-based, controlled cohort study. Participants were children (< 19 years) with unilateral perinatal stroke (arterial ischemic stroke [AIS] or periventricular venous infarction [PVI]), anatomical magnetic resonance imaging (MRI) > 6 months of age, symptomatic hemiparetic cerebral palsy, and no additional neurologic disorders. Typically developing controls had comparable age and gender proportions. T1-weighted anatomical scans were parcellated into 99 regions of interest followed by generation of regional volumes. The primary outcome was thalamic volume expressed as ipsilesional (ILTV), contralesional (CLTV) and thalamic ratio (CLTV/ILTV). Standardized clinical motor assessments were correlated with thalamic volume metrics.

Results: Fifty-nine participants (12.9 years old \pm 4.0 years, 46% female) included 20 AIS, 11 PVI, and 28 controls. ILTV was reduced in both AIS and PVI compared to controls ($p < .001$, $p = .029$, respectively). Ipsilesional thalamic diaschisis was not associated with clinical motor function. However, CLTV was significantly larger in AIS compared to both controls and PVI ($p = .005$, $p < .001$, respectively). CLTV was inversely correlated with all four clinical motor assessments (all $p < .003$).

Conclusion: Bilateral thalamic volume changes occur after perinatal stroke. Ipsilesional volume loss is not associated with clinical motor function. Contralesional volume is inversely correlated with clinical motor function, suggesting the thalamus is involved in the known developmental plasticity that occurs in the contralesional hemisphere after early unilateral injury.

1. Introduction

Perinatal stroke is the leading cause of hemiparetic cerebral palsy (HCP) and affects thousands of Canadian children and their families (Oskoui et al., 2013). Outcomes are often poor with morbidities that last a lifetime (Dunbar and Kirton, 2018). As a focal cerebrovascular lesion, perinatal stroke represents an ideal model for understanding developmental neuroplasticity following early unilateral injury (Craig et al., 2019; Zewdie et al., 2016). Perinatal stroke includes six classifiable disease states but three subtypes predominate (Dunbar and Kirton, 2018). Arterial ischemic stroke (AIS) is usually secondary to occlusion of the middle cerebral artery (MCA), leading to large,

combined cortical and subcortical lesions acquired near term (Dunbar and Kirton, 2018; Kirton and deVeber, 2009). In contrast, periventricular venous infarction (PVI) is a fetal, subcortical lesion that presents in infancy as HCP (Kirton et al., 2010). Common to both subtypes is damage to the motor system, including the corticospinal tracts (Kirton, 2013; Kirton and deVeber, 2009).

The combination of preclinical and human brain mapping studies has generated increasingly informed models of how the motor system develops following unilateral brain damage in the fetus or newborn (Eyre, 2007; Staudt, 2007). Such models have in turn defined central targets for neuromodulation trials in children with HCP (Gillick et al., 2014, 2018; Kirton et al., 2016a, 2017). With a focus on the motor

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cortex, early evidence of efficacy suggests this approach may be fruitful. However, missing from these models are other key brain areas involved in sensorimotor function. For example, recent robotic and imaging studies in children with perinatal stroke have demonstrated the importance of sensory pathways and functions including proprioception and kinesthesia in determining disability (Kuczynski et al., 2016, 2017b; Kuczynski et al., 2017a; Kuczynski et al., 2018). There is therefore a need to explore the contributions of additional brain regions altered by perinatal stroke to better inform developmental models.

Less understood still is how key sensorimotor networks and structures remote from injury are disrupted after early stroke. Leading examples include the cerebellum and thalamus. While direct damage to these structures does not occur with typical lesions, their high connectivity to injured areas may result in structural and functional alterations (Baron et al., 1981; Infeld et al., 1995; De Reuck et al., 1995; Kim et al., 1997; Lin et al., 2009). Such distant changes were termed diaschisis by Von Monakow over 100 years ago and have since been described in a variety of brain regions following stroke (Monakow, 1914). While acute diaschisis may involve changes in blood flow or metabolism, chronic diaschisis mechanisms are largely unknown (De Reuck et al., 1995; Lin et al., 2009). Contralesional or “crossed” cerebellar atrophy following supratentorial infarction is well described in adults and recently demonstrated in pediatric stroke (Baron et al., 1981; Chakravarty, 2002; Craig et al., 2018; De Reuck et al., 1995; Infeld et al., 1995; Kim et al., 1997; Lin et al., 2009; Mah et al., 2013).

Despite being a collection of key nodes within the sensorimotor network, the role of the thalamus in perinatal stroke has barely been studied. As lesions of the anterior circulation (AIS) or medullary venous system (PVI), perinatal strokes do not usually directly injure the major structures of the thalamus. With its high connectivity to areas commonly damaged by perinatal stroke suggests that thalamic diaschisis likely occurs. A recent diffusion imaging study in pediatric stroke suggested the thalamus is the most common location for acute diaschisis to be observed (Kirton et al., 2016b). Investigations of thalamic diaschisis in adult stroke have been limited (De Reuck et al., 1995; Reidler et al., 2018; Sakashita et al., 1993). While chronic cerebellar diaschisis is hypothesized to be due to a loss of excitatory input from the cortico-ponto-cerebellar white matter pathway, the cause of secondary volume changes in thalamic diaschisis are largely unknown (De Reuck et al., 1995; Sakashita et al., 1993). That sensorimotor changes often occur in both hemispheres after perinatal stroke further supports the need to understand the role of the thalamus as a key component of the functional networks required to advance therapeutic rehabilitation approaches.

Therefore, the current study attempted to answer two main questions: (1) does thalamic diaschisis occur following perinatal stroke, and

(2) is thalamic diaschisis associated with clinical motor function.

2. Methods

This was a population-based, retrospective, controlled cohort study.

2.1. Participants

Children aged 6 to 19 years were identified from the Alberta Perinatal Stroke Project, a population-based research cohort (Cole et al., 2017). Inclusion criteria were: 1) Magnetic resonance imaging (MRI) confirmed unilateral arterial (neonatal arterial ischemic stroke, NAIS; arterial presumed perinatal ischemic stroke, APPIS) or venous (periventricular venous infarction, PVI) perinatal stroke; 2) confirmed HCP by a pediatric neurologist (self-described symptoms by children and parents to a pediatric neurologist [AK]); 3) no additional neurological disorder; 4) informed consent/assent. Exclusion criteria were: 1) extensive imaging artifacts or subject motion, 2) additional neurologic abnormalities, 3) severe hemiparesis or spasticity (Manual Ability Classification System V; modified Ashworth scale > 3), and 4) direct injury to the thalamus by visual confirmation on MRIs. Stroke classification was based on established clinical and radiographic criteria by the same experienced investigator (AK) (Kirton et al., 2008). Right-handed typically developing controls (TDC) with comparable proportions of age and gender were identified through the Healthy Infants and Children's Clinical Research Program (HICCUP, www.hiccupkids.ca), an established community-based pediatric research program. This study was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

2.2. Neuroimaging protocol

Participants completed an established neuroplasticity MRI protocol at the Alberta Children's Hospital on a GE 3 Tesla MR750w pediatric research scanner using a 32-channel head coil. High resolution T1-weighted anatomical images were acquired in the axial plane (1 mm isotropic voxels, TR = 8.6 ms, TE = 3.2 ms, flip angle = 11°, FOV = 256 mm). Images were reoriented to consistently place lesions on the left side for all cases to facilitate group comparisons. Images then underwent cortical surface extraction (CSE) and segmentation using established software (BrainSuite version 18a, UCLA (Shattuck and Leahy, 2002)) which removes the skull and classifies tissues into three types: cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) (Shattuck et al., 2001).

Brain images were then parcellated into 99 regions of interest (ROIs) via the SVReg function using the BrainSuiteAtlas1 atlas (Fig. 1)

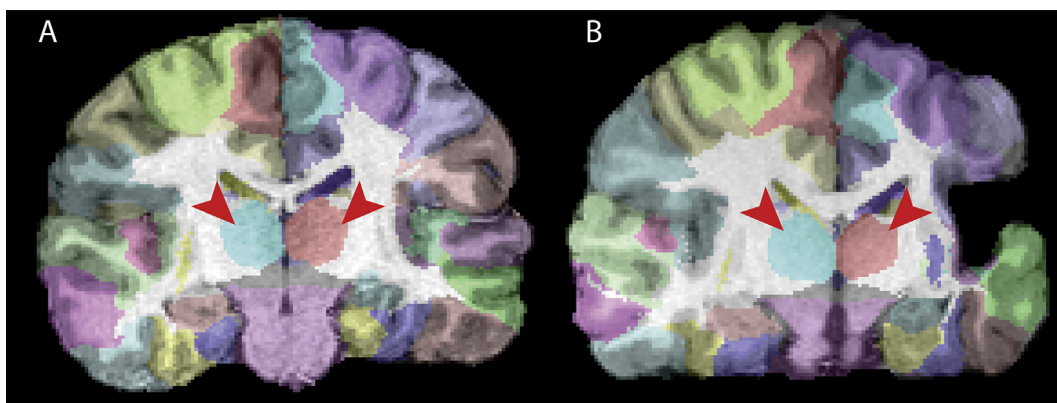


Fig. 1. Parcellation of T1 images.

T1-weighted anatomical scans were parcellated into 99 regions of interest using BrainSuite. Shown are parcellation results in single TDC (A) and AIS (B) participants. Arrows indicate the contralesioned thalamus (light blue) and ipsilesional thalamus (light red). Contralesioned thalamus was classified as the left (i.e. dominant) thalamus in TDC. Both images are portrayed in radiological convention. TDC – typically developing control, AIS – arterial ischemic stroke.

Table 1
Patient demographics and clinical motor outcomes.

Demographics	AIS	PVI	All stroke	Controls
Sex				
Male	N = 11	N = 7	N = 18	N = 14
Female	N = 9	N = 4	N = 13	N = 14
Total	N = 20	N = 11	N = 31	N = 28
Age (SD)	13.3 (4.2)	11.6 (4.8)	13.2 (3.8)	13.1 (3.6)
Side of Stroke (MRI)				
Left (%)	12 (60%)	6 (55%)	18 (58%)	–
Raw thalamic volumes in voxels³ (SD)				
CLTV/dominant	6411 (876)	5847 (342)	6208 (771)	6120 (501)
ILTV/Non-dominant	4689 (990)	5342 (483)	5099 (789)	6129 (625)
Corrected thalamic volumes (SD)				
^a Corrected CLTV/dominant	6.19 (1.0)	5.09 (0.3)	5.78 (0.5)	5.35 (0.4)
^a Corrected ILTV/non-dominant	4.46 (0.8)	4.87 (0.3)	4.55 (0.6)	5.35 (0.6)
Arterial classification				
Middle cerebral artery				
Proximal M1	7 (35%)	–	–	–
Distal M1	11 (55%)	–	–	–
Anterior trunk	1 (5%)	–	–	–
Posterior trunk	1 (5%)	–	–	–
Basal Ganglia involvement	7 (35%)	–	–	–
Motor outcomes				
AHA				
Completed	N = 15	N = 9	N = 24	–
Score out of 88 (SD)	62.3 (19.5)	74.3 (14.5)	66.8 (18.4)	–
MA				
Completed	N = 4	N = 15	N = 19	–
Score out of 100% (SD)	65.5 (25.9)	62.2 (19.5)	62.9 (20.2)	–
BBTA				
Completed	N = 15	N = 9	N = 24	–
# of Blocks (SD)	21.5 (16.7)	33.1 (11.3)	25.8 (15.7)	–
BBTU				
Completed	N = 15	N = 9	N = 24	–
# of Blocks (SD)	49.5 (10.3)	50.3 (16.4)	49.8 (12.6)	–
JTHFA				
Completed	N = 7	N = 5	N = 12	–
Seconds to complete task (SD)	409 (251)	158 (65)	333 (243)	–
JTHFU				
Completed	N = 7	N = 5	N = 12	–
Seconds to complete task (SD)	55.0 (16.8)	68.6 (44.3)	66.8 (43)	–

Note: AIS – arterial ischemic stroke, PVI – periventricular venous infarction, SD – standard deviation, MRI – magnetic resonance imaging confirmed lesion side, CLTV – contralesional thalamic volume, ILTV – ipsilesional thalamic volume, AHA – Assisting Hand Assessment, MA – Melbourne Assessment of Upper Limb Function, BBTA – Box and Blocks Affected, BBTU – Box and Blocks Unaffected, JTHFA – Jebsen Taylor Hand Function Affected, JTHFU – Jebsen Taylor Hand Function Unaffected.

^a Corrected volumes refer to dividing the respective thalamic volume by the total intracranial volume and multiplying it by 1000.

(Joshi et al., 2012). Subsequently, ipsilesional (ILTV) and contralesional (CLTV) thalamic volumes were extracted as the primary imaging outcomes of interest. Total intracranial volume (ICV) was calculated (ICV = GM + WM + CSF volumes). To correct for variability of brain size between participants, thalamic volumes (i.e. ipsi- and contralesional) were divided by total intracranial volume (ICV) and multiplied by 1000 for ease of assessment. Resulting corrected values were used in subsequent analyses and such corrected volumes will be referred to as ILTV and CLTV from now on. Additionally, the thalamic volume ratio (TVR) was calculated on corrected values by dividing the ILTV by the CLTV where values < 1 quantify the degree to which the ipsilesional thalamus was smaller than the contralesional thalamus. For controls,

the dominant left hemisphere was considered analogous to the non-lesioned hemisphere of stroke cases. Volumes were expressed in mm³.

Lesion volumes were calculated for each stroke type. For AIS, a binary lesion mask was created in native T1-anatomical space within MRIcron (Rorden et al., 2007). This semi-automated 3D process fills a specified lesioned area (based on image intensity) until the image encounters a differing intensity suggesting the border of the lesion. Binary masks were then reviewed slice-by-slice and manually edited to ensure accuracy of previous steps and stroke volume in cm³ was extracted. Here, volumes for AIS included only the lesion and not associated areas of ex vacuo ventricular dilatation. PVI volumes were calculated using the relative ventricular asymmetry method whereby the volume of the non-lesioned ventricle is subtracted from lesioned ventricle as described previously (Li et al., 2012).

2.3. Clinical motor assessments

Stroke participants completed four validated motor assessments. The Melbourne Assessment (MA) is a 16-item test that assesses unilateral upper limb movement in children with HCP including grasping, reaching, and manipulation with scores expressed out of 100 (Randall et al., 2014). The Assisting Hand Assessment (AHA) is an evidence-based, validated measure of bimanual upper-extremity function in children with HCP. Participants completed 22 bimanual actions where the affected hand is evaluated for actions such as general use, grasp and release, fine motor adjustments, coordination, and pace. Total scores from 88 are expressed as AHA logit units with a maximum score of 100 (Krumlinde-Sundholm, 2012). The Box and Block Test (BBT) is a measure of unilateral gross manual dexterity testing both the affected (BBTA) and unaffected (BBTU) hands. The score is the number of blocks moved from one side of a box, over a partition, to placement in another box within 60 s (Mathiowetz et al., 1985). Higher scores on the MA, AHA, BBTA and BBTU indicate better performance. The Jebsen Taylor Hand Function (JTHF) Test assesses affected (JTHFA) and unaffected (JTHFU) upper extremity function using daily living activities, such as turning over playing cards, stacking checkers pieces, or picking up small common objects and putting them in a container. Scores are calculated as the total time it takes to complete all tasks meaning lower scores reflect better function (Elizabeth Reedman et al., 2015).

2.4. Analysis

Shapiro-Wilk tests of normality were completed separately for each group. Non-parametric Kruskal-Wallis tests were used to examine differences in means between groups with post hoc Bonferroni corrections to investigate specific differences between the different groups. Pearson (parametric) or Spearman (nonparametric) correlations were used to assess the relationship between thalamic volumes and clinical motor function controlling for age. Cohen's *d* (*d*) was used to calculate the effect size of significant results. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 25.

For the above analysis, both raw and corrected thalamic volumes were tested separately to assess differences in statistical outcomes between the raw thalamic volumes and our corrected volumes, which account for total intracranial volume.

3. Results

3.1. Population

The study population is summarized in Table 1. Of 67 potential participants, eight were excluded due to poor image quality from extensive head motion during the MRI. The final sample consisted of 59 participants (PVI *N* = 11, age = 11.6 ± 4.8 years; 64% male; AIS *N* = 20, age = 13.3 ± 4.2 years; 55% male; TDC *N* = 28, age = 13.1 ± 3.6 years; 50% male). Mean age at the time of imaging

across all groups was 12.9 ± 4.0 years (range = 6.5–19.7).

3.2. Raw and corrected thalamic volumes

All further mentioned statistical tests were completed using raw thalamic volumes, and again with the corrected thalamic volumes. Results revealed that there were no changes in significance between all tests using either method (i.e. raw or corrected). As we believe using the corrected version best accounts for the wide variance in age in our population, we will use the corrected version to explain all results.

3.3. Thalamic volumes within subjects

Healthy controls demonstrated no significant difference between the corrected dominant left ($5.35 \pm 0.4 \text{ mm}^3$) and corrected non-dominant right ($5.35 \pm 0.6 \text{ mm}^3$) thalamic volumes ($p = .945$), resulting in a mean TVR close to 1.0 (1.003 ± 0.05 , $p = .937$).

The AIS group demonstrated significantly smaller mean volumes of the corrected ipsilesional (ILTV = $4.46 \pm 0.8 \text{ mm}^3$) as compared to the corrected contralesional (CLTV = $6.19 \pm 1.0 \text{ mm}^3$) thalamus ($t = 7.364$, $p < .001$, $d = 1.88$). Accordingly, mean TVR was significantly < 1.0 (0.734 ± 0.13 ; $p < .001$).

The PVI group also showed significantly smaller mean thalamic volumes in the corrected ipsilesional hemisphere (ILTV = $4.87 \pm 0.3 \text{ mm}^3$) as compared to the corrected contralesional thalamus (CLTV = $5.09 \pm 0.3 \text{ mm}^3$; $t = 2.328$, $p = .042$, $d = 0.67$). Mean TVR was significantly < 1.0 (TVR = 0.959 ± 0.06 ; $p = .034$).

Corrected ILTV and CLTV were not correlated with each other in the stroke groups ($r = 0.116$, $p = .371$) but were highly correlated within the TDC group ($r_s = 0.824$, $p < .001$). Stroke volume did not correlate with contralesional thalamic volume ($r_s = 0.262$, $p = .207$) but was moderately, inversely correlated with ipsilesional thalamic volume ($r_s = -0.488$, $p = .013$).

3.4. Thalamic volumes between groups

Thalamic volume outcomes between groups are summarized in Fig. 2. Ipsilesional thalamic volumes differed between groups ($H(2) = 18.28$, $p < .001$, Fig. 2A). Pairwise comparisons revealed that controls had higher mean ILTV compared to AIS ($p < .001$; $d = 1.27$). PVI also had lower mean ILTV compared to TDC ($p = .029$, $d = 1.05$) but this did not survive Bonferroni correction ($p = .08$). There was no significant difference between AIS and PVI ILTV ($p = .220$).

Contralesional thalamic volumes were also different across the three groups ($H(2) = 18.28$, $p < .001$; Fig. 2B). AIS had a significantly larger mean CLTV compared to both TDC ($p = .005$; $d = 1.15$) and PVI groups ($p = 0 < 0.001$, $d = 1.64$; Fig. 2B).

Mean TVR differed between the three groups ($H(2) = 36.52$, $p < .001$; Fig. 2C). The AIS group had lower mean TVR as compared to both PVI ($p = .001$, $d = 2.22$) and controls ($p < .001$, $d = 2.73$) There was no difference in TVR between controls and the PVI group ($p = 1.00$).

3.5. Thalamic volumes and clinical motor function

Twenty-four participants completed the MA, AHA, and BBT (median age 14.25 ± 4.0 years, 42% female). Twelve completed the JTHF test.

Unimanual performance as assessed by the MA was negatively correlated with CLTV ($r = -0.599$, $p = .003$) such that larger CLTV was associated with poorer performance (Fig. 3A). In contrast, ILTV was not associated with MA performance ($r = 0.335$, $p = .118$; Fig. 3B). TVR was positively correlated with MA scores ($r = 0.597$, $p = .003$) such that a ratio closer to 1.0 corresponded with better MA performance (Fig. 3C).

Bimanual motor function as assessed by the AHA demonstrated similar correlations to thalamic volumes. CLTV was negatively correlated with AHA scores ($r = -0.471$, $p = .023$) such that higher CLTV was associated with lower AHA performance (Fig. 4A). ILTV did not correlate with AHA scores ($r = 0.270$, $p = .213$; Fig. 4B). TVR was positively correlated with AHA scores ($r = 0.509$, $p = .013$) such that higher thalamic volume ratios corresponded with better function (Fig. 4C).

Performance on the BBT demonstrated similar associations with thalamic volumes. CLTV was inversely correlated with BBTA ($r = -0.540$, $p = .008$) such that a lower CLTV was associated with better performance (Fig. 5A). TVR was positively correlated with BBTA ($r = 0.529$, $p = .009$) such that a more symmetric score corresponded to better BBTA performance (Fig. 5C). ILTV demonstrated no relationship with BBTA ($r = 0.363$, $p = .089$; Fig. 5B). No association was observed between any thalamic volumetric measure and the BBTU.

Finally, CLTV was positively correlated with JTHFA ($r = 0.713$, $p = .009$) such that a larger CLTV was associated with higher scores (lower performance) on the JTHFA. JTHFA was not associated with either ILTV ($r = -0.291$, $p = .359$) or TVR ($r = -0.206$, $p = .520$). No association was observed between thalamic volume measures and JTHFU.

4. Discussion

We have identified and quantified thalamic diaschisis following perinatal stroke and explored its relationship to clinical motor outcomes. Regardless of stroke type, ipsilesional thalamic volumes were reduced, but the degree was not associated with motor outcome. However, we have discovered that contralesional thalamic volumes are

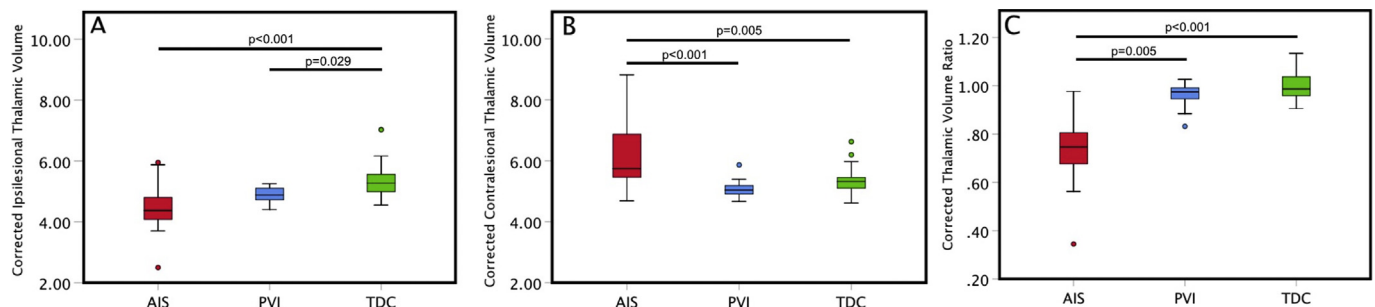


Fig. 2. Thalamic volumetric analyses.

(A) AIS and PVI ILTV was significantly smaller than control non-dominant thalamic volume. (B) AIS CLTV was significantly larger than PVI CLTV and control dominant thalamic volume. (C) AIS TVR was significantly lower than PVI TVR and control TVR.

AIS – arterial ischemic stroke, PVI – periventricular venous infarction, TDC – typically developing control, CLTV – contralesional thalamic volume, ILTV – ipsilesional thalamic volume, TVR – thalamic volume ratio.

Note: Corrected volumes refer to thalamic volumes divided by intracranial volume, then multiplied by 1000.

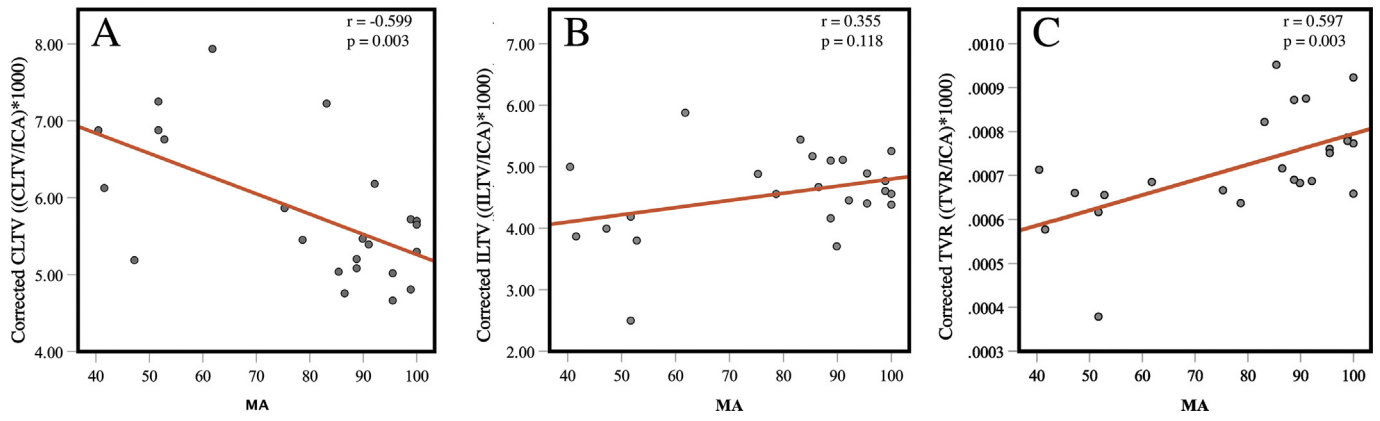


Fig. 3. Melbourne assessment correlations with thalamic volumes.

(A) A significantly negative correlation between CLTV and MA was found. (B) No relationship was found between ILTV and MA. (C) A significantly positive relationship between TVR and MA.

MA – Melbourne Assessment, CLTV – contralesional thalamic volume, ILTV – ipsilesional thalamic volume, TVR – thalamic volume ratio, ICV – intracranial volume.

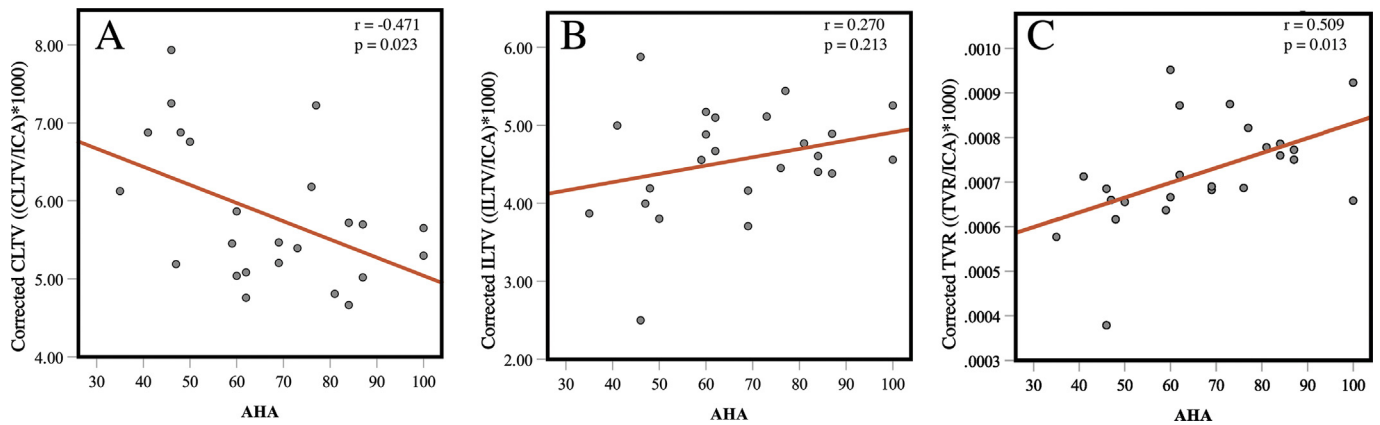


Fig. 4. Assisting Hand Assessment correlations with thalamic volumes metrics.

(A) A significant negative relationship between CLTV and AHA was found. (B) No relationship between ILTV and AHA. (C) A significantly positive correlation between TVR and AHA.

AHA – Assisting Hand Assessment, CLTV – contralesional thalamic volume, ILTV – ipsilesional thalamic volume, TVR – thalamic volume ratio, ICV – intracranial volume.

also altered following perinatal stroke where a robust inverse relationship with clinical motor function was observed. Our results suggest that the thalamus should be considered in evolving models of

developmental plasticity following perinatal stroke.

Our results are consistent with prior studies investigating ipsilesional thalamic diaschisis (ITD) following MCA infarction in adults (De

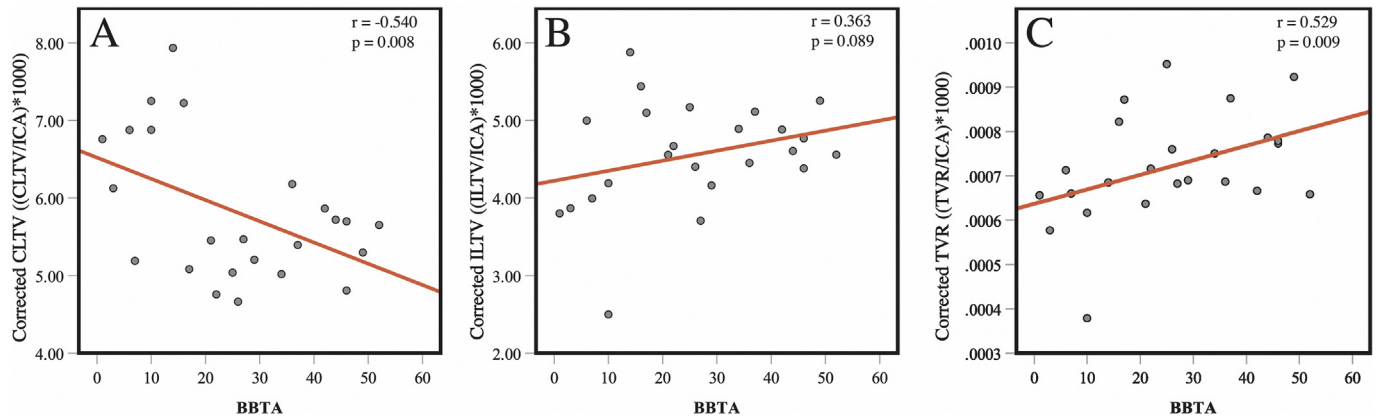


Fig. 5. Box and Blocks Test (Affected hand) correlations with thalamic volume metrics.

(A) A significant negative relationship between CLTV and BBTA. (B) No relationship between ILTV and BBTA. (C) A significant positive relationship between TVR and BBTA.

BBTA – Box and Blocks Affected, CLTV – contralesional thalamic volume, ILTV – ipsilesional thalamic volume, TVR – thalamic volume ratio, ICV – intracranial volume.

Reuck et al., 1995; Reidler et al., 2018; Sakashita et al., 1993). The finding that ipsilesional thalamic volumes were reduced in both AIS and PVI is consistent with degeneration projecting through white matter tracts into areas anatomically connected to but remote from the primary infarct. This holds true for both AIS and PVI suggesting that ipsilesional diaschisis is not limited to the large cortical strokes typical of AIS but also occurs after smaller periventricular white matter injuries. This also suggests that the timing of injury, whether it is in utero (PVI) or near term (AIS) does not have a large influence on thalamic diaschisis. The finding that stroke lesion volume was not related to ITD may suggest that lesion location or other variables are more important mediators of diaschisis.

That no clear relationship between ITD and clinical motor outcomes was observed refuted our original hypothesis. However, this relationship has not been well defined in previous stroke studies (Reidler et al., 2018). Although ITD was not statistically related to performance on motor assessments, there was an overall suggestion that less ILTV loss may be associated with better motor ability. Most correlations in this regard fell in the moderate range ($r > 0.30$), suggesting possible clinical significance. In small studies with modest statistical power such as ours, it may be informative to consider such association measures (Chavalarías et al., 2016; Lee, 2016). This small to moderate effect may also be due to the relative insensitivity of the instruments used to measure motor outcomes. While the AHA and MA are designed to measure real-life motor function and maximize external validity (and do so well), they may not be sensitive enough to pick up on subtle sensory or motor dysfunction mediated by ipsilesional thalamic diaschisis.

Our most interesting finding was the identification of what appears to be an important role for the contralesional thalamus in motor system development following perinatal stroke. Contralesional thalami were found to be larger in AIS as compared to TDC and PVI. One possible explanation could relate to the known developmental plasticity that occurs in the contralesional hemisphere following early unilateral injury. As with other elements of sensorimotor system development after perinatal stroke, this does not appear to be mere “compensation” by the contralesional side for a number of reasons. First, volumes of contralesional and ipsilesional thalami were *not* correlated to one another which might be expected if differences were due to positive compensatory mechanisms (i.e. the smaller the ipsi-lesioned thalamus, the larger the contra-lesioned thalamus). Rather, volumes appeared to be independent of each other, suggesting a more complex relationship between the contralesional thalamus and the sensorimotor network, most likely in the same hemisphere. Second, if contra-lesioned thalamus was simply “taking over”, then presumably larger volumes would be adaptive and associated with better function. Our results show the opposite and were strongly consistent revealing that contralesional thalamic volume is inversely correlated with clinical function across all four measures employed. This again may suggest that the degree of need to reorganize function into the contralesional hemisphere may be increased in those with worse motor function, with correspondingly larger volumetric changes in the contralesional thalamus.

So how might our findings here of thalamic changes in the contralesional hemisphere relate to these known patterns of reorganization that often involve the contralesional side of the brain? From the motor perspective, it has been considered that an “extra” motor system must occupy the contralesional hemisphere when such developmental organization occurs. While so-called “crowding theory” remains controversial, many functional imaging and transcranial magnetic stimulation (TMS) studies have shown that the contralesional motor cortex contains distinct regions for ipsilateral motor control (Staudt, 2007; Zewdie et al., 2016). This displaced system likely carries connectivity to the thalamus in the same hemisphere. In a similar regard, the high flow of sensory information through the thalamus to the sensory cortex may also be altered by perinatal stroke (Kuczynski et al., 2017b; Kuczynski et al., 2017a). Using TMS or imaging to better connect such

sensorimotor changes with thalamic volume changes, including parcellation of thalamic nuclei and or connectivity imaging methods such as resting state fMRI, may provide valuable insight to better understand why contralesional thalamic volumes are altered and clinically relevant.

Our findings further highlight the need to explore additional components of the motor network and how they are altered after perinatal stroke. In addition to the thalamus and the motor and sensory nodes outlined above, a recent study describing volumetric changes in the ipsilesional cerebellum add an additional component (Craig et al., 2018). With known projections to the contralesional thalamus via the dentato-rubro-thalamo-cortical tract, that both the current study and the cerebellar study found correlations with motor function suggests a possible connection as well as clinical relevance (Craig et al., 2018). Even with these studies filling out perinatal stroke models, other key components of the motor network remain virtually unexplored including prefrontal motor cortex and the basal ganglia.

Several significant limitations in our study should be considered. Our sample had a wide age range (6–19 years) in order to reflect relevant populations but also introduces variance in regards to brain volumes, developmental effects and performance on outcome measures. We attempted to control for this by correcting thalamic volumes using total intracranial volume and all correlations were completed using partial correlations controlling for age. Our anatomical imaging only allowed examination of thalamic and lesion volumetrics. Future studies could further investigate how functional, structural, and metabolic changes are related to thalamic changes in perinatal stroke (Carlson et al., 2017; Ilves et al., 2016). Higher resolution imaging could permit a more in-depth parcellation of the thalamus to explore which specific thalamic nuclei are altered following stroke. Our sample of perinatal stroke participants contained more males than females and more left strokes than right strokes, but this represents the natural occurrence of the disease. We restricted our sample to relatively high-functioning children who were able to tolerate a lengthy MRI with minimal head motion and this selection bias may make our results less representative of the most severely affected children with perinatal stroke. Additionally, not all participants completed the full battery of motor assessments.

5. Conclusion

Bilateral thalamic volume changes occur after perinatal stroke. Ipsilesional volume loss is not associated with clinical motor function. Contralesional volume is inversely correlated with clinical motor function, suggesting the thalamus is involved in the known developmental plasticity that occurs in the contralesional hemisphere after early unilateral injury.

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Disclosures

None.

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