Quantitative comparison of cortical and deep grey matter in pathological subtypes of unilateral cerebral palsy

SIMON M SCHECK[1,2] | KERSTIN PANNEK[1,2,3] | SIMONA FIORI[4] | ROSLYN N BOYD[2] | STEPHEN E ROSE[3]

1 The University of Queensland, School of Medicine, Brisbane, Qld; **2** Queensland Cerebral Palsy and Rehabilitation Research Centre, Brisbane School of Medicine, The University of Queensland, Brisbane, Qld; **3** Centre for Computational Informatics, CSIRO, Australian e-Health Research Centre, Brisbane, Qld, Australia. **4** IRCCS Stella Maris, Calambrone, Pisa, Italy.

Correspondence to Stephen Rose, Australian e-Health Research Centre, Level 5, UQ Health Sciences Building, Royal Brisbane and Women's Hospital, Herston, QLD 4029, Australia. E-mail: Stephen.Rose@csiro.au

PUBLICATION DATA
Accepted for publication 17th February 2014.
Published online 19th April 2014.

ABBREVIATIONS

CDGM	Cortical or deep grey matter
CTD	Children with typical development
JTHFT	Jebsen-Taylor Hand Function Test
PWM	Periventricular white matter
UCP	Unilateral cerebral palsy
VBM	Voxel-based morphometry

AIM The aim of this study was to quantify grey matter changes in children with unilateral cerebral palsy (UCP), differentiating between cortical or deep grey matter (CDGM) lesions, periventricular white matter (PWM) lesions, and unilateral and bilateral lesions.
METHOD In a cross-sectional study we obtained high resolution structural magnetic resonance images from 72 children (41 males, 31 females, mean age 10y 9mo [SD 3y 1mo], range 5y 1mo–17y 1mo) with UCP (33 left, 39 right hemiplegia; Manual Ability Classification System level I n=29, II n=43; Gross Motor Function Classification System level I n=46, II n=26), and 19 children with typical development (CTD; eight males, 11 females, mean age 11y 2mo [SD 2y 7mo], range 7y 8mo–16y 4mo). Images were classified by lesion type and analyzed using voxel-based morphometry (VBM) and subcortical volumetric analysis.
RESULTS Deep grey matter volumes were not significantly different between children with CDGM and PWM lesions, with the thalamus, putamen, and globus pallidus being reduced unilaterally in both groups compared with CTD ($p \leq 0.001$). Children with CDGM lesions additionally showed widespread cortical changes involving all lobes using VBM ($p<0.01$). Children with bilateral lesions had reduced thalamus and putamen volumes bilaterally ($p<0.001$). The thalamic volume was reduced bilaterally in children with unilateral lesions ($p=0.004$).
INTERPRETATION Lesions to the PWM cause secondary changes to the deep grey matter structures similar to primary changes seen in CDGM lesions. Despite having a unilateral phenotype, grey matter changes are observed bilaterally, even in children with unilateral lesions.

Cerebral palsy (CP) is a heterogeneous group of non-progressive brain injuries manifesting primarily as motor impairments. The diagnosis is made clinically, based on common motor phenotypes: spasticity, dyskinesia, and ataxia.[1] Underlying the phenotype are heterogeneous pathological features, that relate to the timing and aetiology of the insult: brain malformations originating in the first or second trimester; white matter lesions, typically arising early in the third trimester, most often in preterm children; and grey matter lesions typically arising late in the third trimester.[2]

Children with grey matter lesions have more severe motor impairment than other subtypes,[3] particularly when both the thalamus and basal ganglia are involved.[4] This may be because of a reduced potential for plasticity within thalamocortical projections compared with corticomotor projections.[5] Thalamic changes are not limited to children with primary grey matter lesions; reduction in the thalamic volume without morphological or organisational change is also seen in children with periventricular white matter (PWM) lesions.[6,7]

Unilateral CP (UCP) is a clinical subgroup caused by either unilateral or bilateral lesions. Up to half of children with UCP have bilateral lesions (primarily children with PWM lesions), despite having unilateral clinical features.[4,8]

Quantitative assessment of grey matter using magnetic resonance imaging (MRI) can be carried out using several techniques. Application of such techniques to abnormal brain images poses a significant challenge. Voxel-based morphometry (VBM) is one approach, involving registration of participant brains to a standard space allowing group wise analysis of grey matter within each voxel.[9] VBM is most reliable where the grey-white interface is distinct, and signal to noise ratio is high, particularly the cortex. Cortical motor and sensory as well as thalamic and basal ganglia changes have been identified in children with spastic diplegia using this technique.[10] VBM is less reliable in deep grey matter, particularly the thalamus, where the

 DOI: 10.1111/dmcn.12461

grey-white interface is less distinct.[11] An alternative approach is segmentation of specific structures using probabilistic deformation of predefined structural templates.[11,12] This technique relies on statistical mapping to predefined models and, therefore, also becomes less reliable where brain morphology is abnormal. Whole brain surface-based parcellation techniques are often unable to process images adequately with abnormalities interfering with cortical continuity, such as middle cerebral artery infarcts or schizencephaly. One solution is to analyze only the subcortical structures.[11]

The aim of the present study was to quantify differences in both cortical and deep grey matter between subtypes of UCP. It utilized automated techniques to quantify the extent of grey matter change in children with UCP, and specifically to compare subcortical structure volumes and morphology between children with secondary subcortical damage caused by PWM lesions and children with direct subcortical damage from CDGM lesions. We hypothesized that subcortical structures, in particular the thalamus, would be reduced in volume similarly across all subtypes of UCP, despite heterogeneous aetiology. To assess grey matter changes in children with UCP, we employed two techniques. To analyze cortical and subcortical differences between groups we used VBM. For a more robust analysis of the deep grey matter structures we additionally employed volumetric segmentation analysis.

METHOD

Participants

Participants were identified through a population-based research database, comprising of children with CP known to the Queensland Cerebral Palsy and Rehabilitation Research Centre, the Queensland Cerebral Palsy Register, and Queensland CP Health Service, as well by advertising to occupational therapists, physiotherapists, and paediatricians at the Royal Children's Hospital, Brisbane and in the community. Participants included 72 children with UCP (41 males, 31 females, mean age 10y 9mo [SD 3y 1mo], range 5y 1mo–17y 1mo; 33 left, 39 right hemiplegia), all of whom were recruited for clinical studies requiring baseline MRI and clinical assessment before intervention. Inclusion criteria were children with a diagnosis of UCP, attending mainstream school and able to ambulate unaided. All children were assessed by an occupational therapist using the Gross Motor Function Classification System (GMFCS)[13] (I=46, II=26) and the Manual Ability Classification System (MACS)[14] (I=29, II=43). Nineteen CTD, without brain pathology or indication for imaging were also recruited for the MRI protocol (eight males, 11 females, mean age 11y 2mo [SD 2y 7mo], range 7y 8mo–16y 4mo). The Jebsen-Taylor Hand Function Test (JTHFT) was used to assess both dominant and impaired hand function in 64 of the children with CP (30 left, 34 right hemiplegia). This is a unimanual measure of speed and dexterity in everyday tasks where lower scores represent faster performance in seconds.[14] The study was approved by the Ethics in Human Research Committees at the Royal Children's Hospital, Brisbane and The University of Queensland, Brisbane (EHREC 41 and RCH 37). All parents/guardians gave written informed consent, and children gave verbal assent. Participants were given the opportunity to attend a mock scanning before imaging.

What this paper adds

- Congenital white matter lesions affect grey matter volume.
- Deep grey matter nuclei volumes are similar across unilateral cerebral palsy (UCP).
- Grey matter changes are evident bilaterally in UCP.

Image acquisition

High-resolution structural images were acquired for each participant using a $0.9mm^3$ isotropic 3D T1-weighted magnetization-prepared gradient-echo (MPRAGE) sequence in a 3T MRI scanner (Siemens, Erlangen, Germany). The acquisition parameters were: FOV 24 x 25.6 x 17.6cm, TR/TE/TI 2300/2.26/900ms, flip angle 9°, with 0.9mm isotropic resolution.

Image classification

Images were qualitatively assessed by a child neurologist (SF) according to a qualitative system[1] as either cortical or deep grey matter lesions (CDGM), PWM lesions, brain malformations, or miscellaneous. Each lobe and deep grey matter structure in each hemisphere was then systematically assessed for abnormalities, allowing a classification of each lesion as either unilateral (i.e. all abnormalities constrained to one hemisphere) or bilateral. For simplicity, we use the terminology 'dominant' and 'non-dominant' hemisphere, where the hemisphere contralateral to the side of impairment is considered non-dominant (functional dominance was not assessed in this study, and therefore what we refer to as the dominant hemisphere is not necessarily functionally dominant).

Voxel-based morphometry

Structural images were analyzed using FSL-VBM, contained within FMRIB's Software Library (FSL: http://www.fmrib.ox.ac.uk/fsl).[15] Brain extraction and grey matter segmentation were performed, followed by non-linear registration to a study-specific grey matter template in standard space. Templates were created using equal numbers of children with and without UCP, with a specific template being created for each analysis. Registered grey matter images were then modulated using the Jacobian of the warp field, smoothed with an isotropic Gaussian kernel (σ=3mm). Output from each stage was visually assessed. A voxel wise general linear model was employed to account for age and sex. Voxels with significantly different grey matter concentration between the children with UCP and the CT were identified using a voxel wise permutation-based independent-sample *t*-test within the model, using the 'randomize' function within FSL. A similar model was employed to identify voxels in which grey matter

concentration was related to JTHFT scores. All analyses were adjusted for multiple comparisons across space using threshold-free cluster enhancement (TFCE),[16] considered significant at corrected $p<0.01$. We use the terminology 'grey matter concentration', which refers to the likelihood of a voxel containing grey matter, not a physical property of the underlying grey matter.

Subcortical parcellation and analysis

Deep grey matter structure segmentation was performed using FMRIB's Integrated Registration and Segmentation Tool (FIRST), contained within FSL.[11] Two-stage registration to standard space was performed: 12 degrees of freedom linear transformation followed by a second 12 degrees of freedom linear transformation using a subcortical mask. Segmentation was then carried out using training data included within FSL, derived from 336 participants, including children and adults with both typical and pathological brains. Volumes of the thalamus, putamen, globus pallidus and caudate were reported. Segmentations were visually inspected in native participant space overlaid on T1 images. Where minor errors were noted, segmentations were manually corrected. Any hemisphere containing a major anatomical error was excluded. To control for brain size, total brain volume was calculated.[17]

Statistical analysis of deep grey matter volumes was performed using STATSOFT Statistica, version 12, (StatSoft Inc., Tulsa, OK, USA). General linear models were employed to account for age, sex and total brain volume. JTHFT performance and deep grey matter volumes were compared between unilateral and bilateral lesions, as well as between lesion types. One-way analysis of variance (ANOVA) was used to identify structures with significantly different volumes between groups. Post-hoc analysis was then carried out on significant structures to elicit differences between groups and hemispheres, using Bonferroni correction. As multiple hypotheses were being tested in this study, results were considered significant at $p<0.01$. Relationships between dominant and impaired JTHFT scores and deep grey matter volumes were analyzed using a single general linear model, built using forward stepwise analysis to include only statistically significant variables.

RESULTS

Qualitative description of lesions

PWM lesions were observed in 53 out of 72 children (73.6%). Lesions were unilateral in 32 children (60.4%) and bilateral in 21 (39.6%). CDGM lesions were observed in 17 children (23.6%). Fifteen of these participants (88.2%) showed both cortical and subcortical damage, with the remaining two having isolated subcortical damage. Since this latter group was too small to allow for statistical comparisons, the participants were grouped together in a single cohort. The majority (88.2%) of these CDGM lesions were unilateral, with two children having bilateral involvement (11.8%). Brain malformations were observed in two children (2.8%), and excluded from further analyses because of insufficient numbers. Details are shown in Table I, including abnormalities within the thalamus and lentiform nucleus (comprising the globus pallidus and putamen).

Hand function

JTHFT scores were not significantly different between children with unilateral ($n=21$) and bilateral lesions ($n=43$) ($p=0.017$; bilateral lesions dominant hand mean: 47.1 [95% confidence interval (CI): 38.1–56.2], impaired hand mean: 187.2 [95% CI: 104.5–269.9]; unilateral lesions dominant hand mean: 41.1 [95% CI: 36.6–45.6], impaired hand mean: 262.8 [95% CI: 193.0–332.7]). JTHFT scores were significantly different between children with PWM ($n=47$) and CDGM lesions ($n=15$) ($p=0.007$; CDGM dominant

Table I: Participant characteristics, and number of participants with anatomical abnormalities within the thalamus and lentiform nucleus (putamen and globus pallidus)

													Anatomical abnormalities			
	Lesion		Age				Sex		MACS level		GMFCS level		Thalamus		Lentiform	
Hemiplegia	Type	Extent	*n*	Median	Min	Max	M	F	I	II	I	II	L	R	L	R
Comparison group	None	n/a	19	11.13	7.68	16.3	8	11	–	–	–	–	–	–	–	–
Left	BM	n/a	1	10.01	10.01	10.01	–	1	–	1	–	1	–	–	–	–
	CDGM	Bilateral	0	–	–	–	–	–	–	–	–	–	–	–	–	–
	CDGM	Unilateral	7	11.78	8.08	12.53	4	3	1	6	2	5	–	7	–	5
	PWM	Bilateral	11	10.61	5.09	16.97	7	4	6	5	10	1	–	5	–	3
	PWM	Unilateral	14	8.34	5.45	14.16	8	6	8	6	11	3	–	5	–	5
Right	BM	n/a	1	11.03	11.03	11.03	0	1	1	–	1	–	–	–	–	–
	CDGM	Bilateral	2	12.925	11.94	13.91	1	1	1	1	1	1	2	1	–	–
	CDGM	Unilateral	8	10.415	5.67	17.05	4	4	1	7	3	5	8	–	6	–
	PWM	Bilateral	10	13.1	6.26	16.39	6	4	3	7	7	3	4	–	3	–
	PWM	Unilateral	18	9.675	5.98	15.91	11	7	8	10	11	7	14	–	12	–

BM, brain malformation; CDGM, cortical or deep grey matter lesion; PWM, periventricular white matter lesion; MACS, Manual Ability Classification System; GMFCS, Gross Motor Function Classification System.

hand mean: 41.5 [95% CI: 32.3–50.7], impaired hand mean: 376.9 [95% CI: 234.0–519.8]; PWM dominant hand mean: 43.7 [95% CI: 38.7–48.7], impaired hand mean: 196.6 [95% CI: 142.0–251.2]). Post-hoc analysis showed children with CDGM lesions had significantly higher scores (higher impairment) in the impaired hand only (p=0.010).

Voxel-based morphometry

The 70 included children with UCP were all satisfactorily registered to respective group-specific templates: CDGM (not separated into unilateral and bilateral because of insufficient numbers), unilateral PWM and bilateral PWM. Children with CDGM lesions (n=17) showed widespread unilateral cortical and subcortical changes in both left and right hemiplegia groups (p<0.01 corrected). Cortical reduction in grey matter concentration in children with left hemiplegia was observed in all four lobes in the non-dominant hemisphere, and did not extend to the dominant hemisphere. Deep grey matter changes were also unilateral, involving the entire caudate as well as globus pallidus and medial thalamus. In children with right hemiplegia (n=10, including two bilateral lesions) changes were more pronounced, involving the majority of the caudate, putamen, globus pallidus and thalamus bilaterally, as well as the dorsal anterior cingulate and posterior cingulate bilaterally.

Children with bilateral PWM lesions (n=21) showed minor cortical involvement, with both left and right hemiplegia groups showing reduced grey matter concentration within the medial temporal cortex of the non-dominant hemisphere. Children with left hemiplegia (n=11) additionally showed reduced grey matter concentration within the postcentral gyrus and precuneus. In children with both left and right hemiplegia, deep grey matter changes involved the entire caudate in the non-dominant hemisphere as well as posterior and medial thalamus bilaterally, more pronounced in the non-dominant hemisphere.

Grey matter changes in children with unilateral PWM lesions (n=32) only reached statistical significance in the right hemiplegia group (n=18), showing significant reduction in grey matter concentration in the caudate bilaterally, as well as unilateral changes in the posterior medial thalamus, putamen and extending into the insular cortex.

There were no regions for any analysis where grey matter concentration was lower in the CTD than in the children with UCP. Results are shown visually in Fig. 1.

No voxels were identified where grey matter concentration significantly correlated with JTHFT scores for either hand.

Volumetric analysis

Segmentation

From 72 children with UCP, two scans (2.8%) were unable to be satisfactorily segmented, because of poor registration (n=1) or inaccurate segmentation (n=1). Both excluded children had unilateral CDGM lesions and right hemiplegia. Of the included children, 11 (15.7%) contained unsatisfactory segmentations in the non-dominant hemisphere, and therefore volumes in this hemisphere were excluded (left hemiplegia: unilateral CDGM n=6, bilateral PWM n=1; right hemiplegia: unilateral CDGM n=3, bilateral PWM n=1). The caudate was slightly underestimated bilaterally in seven children (10.0%) and unilaterally in 15 children (21.4%), 12 of which were on the non-dominant side, and were therefore excluded from further analysis. The thalamus was slightly overestimated bilaterally in one child (1.4%) and unilaterally in the non-dominant hemisphere in two children (2.9%). The putamen was slightly underestimated bilaterally in one child (1.4%) and unilaterally in eight children (11.4%), all in the non-dominant hemisphere. In total, 35 scans (50%) were deemed to be entirely free from segmentation inaccuracies. All inaccurate thalamus and putamen segmentations were manually corrected (Fig. S1). Examples of included, corrected and excluded segmentations are shown in Fig. 2. All CTD were segmented appropriately with the exception of one child (5.2%), for whom the caudate was slightly underestimated bilaterally.

Raw volumes and 95% CI are given in the supplementary material before (Table SII) and after (Table SI) manual corrections. Absolute and relative changes due to manual correction are shown in Table SIII. Corrected volumes with 95% CI adjusted for age, gender, and total brain volume are shown in Fig. 3.

Unilateral versus bilateral lesions

Dominant hemisphere deep grey matter volumes were significantly different between controls (n=19) and children with unilateral (n=45) and bilateral (n=25) lesions (p=0.008). Post-hoc analysis showed that compared with controls, children with unilateral lesions had significantly lower volume in the thalamus (p=0.004); children with bilateral lesions had significantly reduced volumes in the thalamus (p<0.001) and putamen (p<0.001). Children with bilateral lesions had significantly reduced volume in the thalamus (p<0.001) and globus pallidus (p=0.006) compared with children with unilateral lesions (volumes with 95% CI shown in Fig. 3). In a sub-analysis of children with unilateral lesions, there was no significant difference in deep grey matter volumes between children with CDGM lesions and PWM lesions in either the dominant (p=0.709; CDGM n=13, PWM n=32) or non-dominant (p=0.068; CDGM n=4, PWM n=32) hemispheres.

Non-dominant hemisphere deep grey matter volumes were also significantly different between CTD (n=19) and children with unilateral (n=36) and bilateral (n=23) lesions (p=0.001). Post-hoc analysis showed children with both bilateral and unilateral lesions had reduced volumes for all structures compared with CTD (p<0.001 for all structures and groups). Children with bilateral lesions had significantly reduced volume in the thalamus (p<0.001) compared

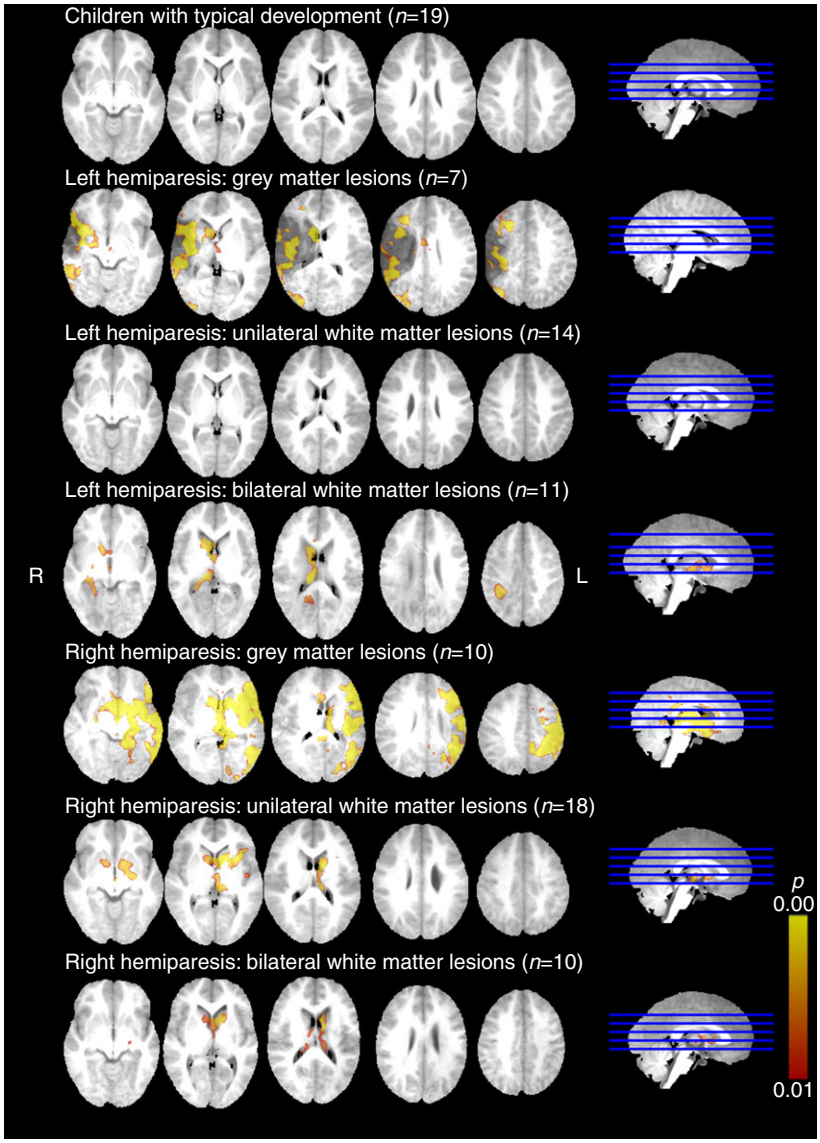

Figure 1: Results of voxel-based morphometry. Highlighted regions indicate significantly lower grey matter concentration within a voxel in participants compared with controls with typical development. For display purposes, results are shown on templates created by combining all participants within each group. Axial slices are taken at the levels shown.

with children with unilateral lesions. Volumes and 95% CI are shown in Fig. 3.

CDGM versus PWM lesions

Dominant hemisphere deep grey matter volumes were not significantly different between CTD (n=19), children with CDGM lesions (n=15), and children with PWM lesions (n=53) (p=0.099). Non-dominant hemisphere deep grey matter volumes were significantly different between CTD (n=19), children with CDGM lesions (n=6), and children with PWM lesions (n=51) (p=0.001). Post-hoc analysis showed that children with CDGM lesions had reduced volumes compared with CTD in the thalamus (p=0.001), putamen (p<0.001), and globus pallidus (p<0.001); children with PWM lesions had reduced volumes compared with CTD in the thalamus (p<0.001), putamen (p<0.001), and globus pallidus (p<0.001). Volumes were not significantly different between children with PWM and CDGM lesions for any structure. JTHFT scores did not significantly correlate with volumes for any structure.

DISCUSSION

The present study utilized two independent, automated analysis techniques to quantify grey matter differences between subtypes of UCP. Results showed that cortical changes are minimal in children with PWM lesions, while deep grey matter changes are not significantly different

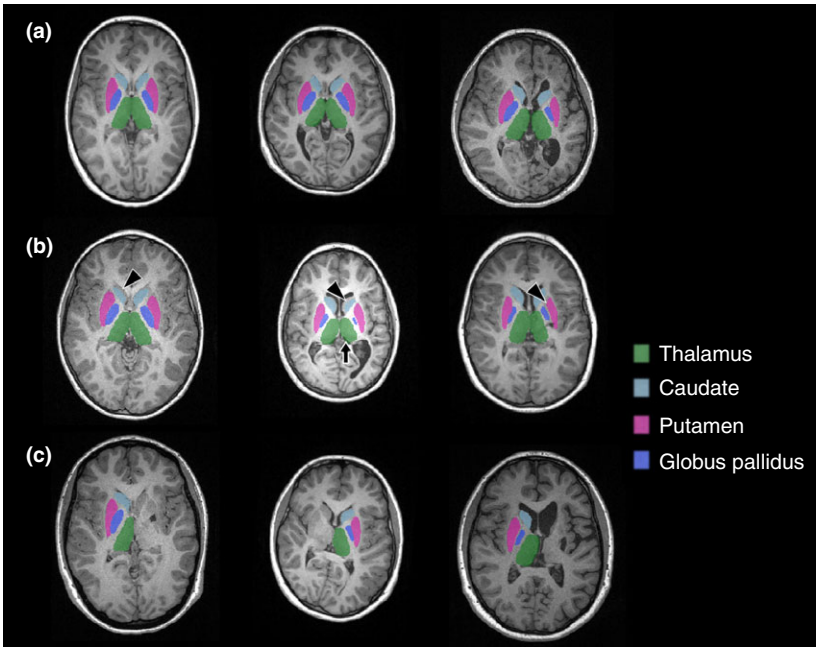

Figure 2: Samples of deep grey volume segmentation in children with unilateral cerebral palsy. (a) Samples of appropriate segmentation; (b) samples of minor errors, which were manually corrected (arrowheads indicate underestimation, arrow indicates overestimation); (c) samples of segmentation where only one hemisphere was able to be accurately segmented.

between CDGM and PWM lesions. In addition, we have demonstrated that 39.6% of lesions are bilateral on MRI, similar to previous studies (Cioni et al.:[8] 55% bilateral [*n*=91]; Holmefur et al.:[4] 37% bilateral [*n*=27]). Children with bilateral lesions had significantly reduced thalamic volumes bilaterally compared with unilateral lesions. In children with unilateral lesions, despite the dominant hemisphere appearing qualitatively normal, mean thalamic volume was reduced compared with CTD. These results highlight the heterogeneity of grey matter changes that underlie UCP, and the similarities between primary and secondary deep grey matter nuclei changes.

The cohort for this study consisted of 73.6% PWM lesions, 23.6% CDGM lesions, and 2.8% brain malformations. This is a greater proportion of PWM lesions than previous studies (36[2]–45%[8]), likely to be because of inclusion of only children able to mobilize unaided (GMFCS levels I and II). Results may therefore differ from children with more severe hemiplegia. CDGM lesions were associated with significantly worse clinical outcomes than PWM lesions, consistent with previous studies.[3] Deep grey matter nuclei volumes were not significantly different between these two subtypes, despite the difference in aetiology. Diffusion MRI has identified reduced integrity of the thalamic radiations in children with CP, correlating with clinical function.[18] This relationship has been demonstrated in children with UCP and PWM lesions, with preservation of topographical organization of fibres within the thalamus.[7] Lesions involving thalamic projections are the most likely cause of secondary reduction in thalamic volume. Similar changes have been observed in children with bilateral impairment caused by PWM lesions.[6] The pathophysiology of these secondary changes to thalamic grey matter differs from that occurring in CDGM lesions, where the primary lesion directly impacts on the grey matter. Children with bilateral PWM lesions also showed a reduction in grey matter in the medial temporal lobe, posterior cingulate and precuneus; all within the default mode network, the most highly structurally and functionally connected network within the brain.[19] Further investigation into the structural and functional connectivity of this network in these children is warranted.

The difference in hand function between children with unilateral and bilateral lesions did not meet statistical significance, similar to previous findings.[4]

The population for this study was sufficiently large to demonstrate several key findings; however, we could not comment on the significance of observed changes in the less common subtype of brain malformations. Adequate segmentation of data for volumes within the non-dominant hemisphere in children with CDGM lesions was limited (*n*=6). The inability to adequately segment highly abnormal brains is a technical limitation, which along with exclusion of the caudate, may cause selection bias towards more typical brains. The requirement for manual correction in a minority of participants was undertaken to minimize this selection bias, at the cost of reduced reproducibility. Thalamic volumes for controls were comparable with studies using both manual[20] and alternative automated techniques (Freesurfer)[21] in children of similar ages.

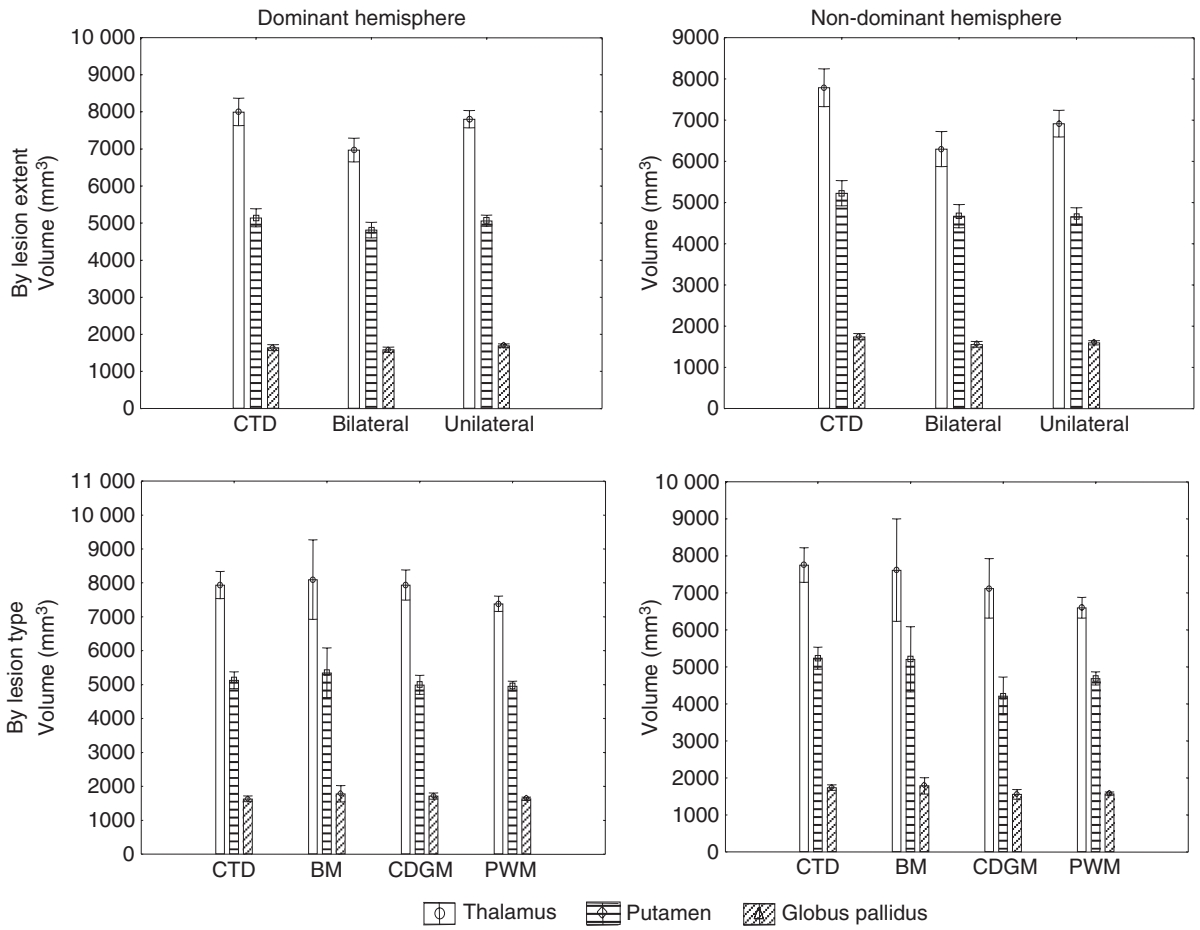

Figure 3: Volumes of deep grey matter nuclei structures in children with typical development (CTD) and children with unilateral cerebral palsy, sorted by unilateral and bilateral lesions, and separately by lesion type (cortical or deep grey matter lesion [CDGM], periventricular white matter lesion [PWM] or brain malformation [BM]). Vertical bars show 95% confidence intervals, corrected for age, sex, and total brain volume.

CONCLUSION

The aetiology of brain injury resulting in UCP is heterogeneous. Lesions may appear unilateral or bilateral qualitatively on MRI, however, even in unilateral lesions, deep grey matter nuclei may be impacted upon bilaterally. We did not identify a significant difference in function between bilateral and unilateral lesions. Lesions occurring primarily in the PWM appear to cause secondary changes to connected grey matter structures, particularly the thalamus and basal ganglia, but may also extend to cortical regions. These secondary changes result in similar volume reduction within the deep grey matter structures to those observed in children with primary CDGM lesions. Children with primary CDGM lesions, however, appear to have significantly worse clinical outcomes, which may be because of more extensive cortical involvement.

ACKNOWLEDGEMENTS

This study is funded by a Career Development Fellowship (RNB) and National Health and Medical Research Council (COMBIT; Project Grant 1003887). SMS is funded by UQRS scholarship at The University of Queensland. We also acknowledge the efforts of occupational therapists Dr Leanne Sakzewski, Kerry Provan, and Joanne Bowden who performed the clinical assessments; statistician Dr Peter Baker for statistical advice; and Julien Savina for administrative contributions. We are grateful to all study participants and parents/guardians for their time and participation. The authors state that they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Volumes of deep grey matter nuclei in children with unilateral cerebral palsy, separated by lesion type.

Table SII: Volumes of deep grey matter nuclei in children with unilateral cerebral palsy, separated by lesion type, before manual correction of thalamus and putamen segmentations.

Table SIII: Relative and absolute changes to thalamus and putamen segmentation volumes with manual corrections.

Figure S1: Samples of manually corrected segmentations of the thalamus and putamen.

REFERENCES

1. Krägeloh-Mann I, Cans C. Cerebral palsy update. *Brain Dev* 2009; **31**: 537–44.
2. Krägeloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol* 2007; **49**: 144–51.
3. Arnfield E, Guzzetta A, Boyd R. Relationship between brain structure on magnetic resonance imaging and motor outcomes in children with cerebral palsy: a systematic review. *Res Dev Disabil* 2013; **34**: 2234–50.
4. Holmefur M, Kits A, Bergstrom J, et al. Neuroradiology can predict the development of hand function in children with unilateral cerebral palsy. *Neurorehabil Neural Repair* 2012; **27**: 72–8.
5. Wilke M, Staudt M, Juenger H, Grodd W, Braun C, Krageloh-Mann I. Somatosensory system in two types of motor reorganization in congenital hemiparesis: topography and function. *Hum Brain Mapp* 2009; **30**: 776–88.
6. Zubiaurre-Elorza L, Soria-Pastor S, Junque C, et al. Thalamic changes in a preterm sample with periventricular leukomalacia: correlation with white-matter integrity and cognitive outcome at school age. *Pediatr Res* 2012; **71**: 354–60.
7. Tsao H, Pannek K, Boyd RN, Rose SE. Changes in the integrity of thalamocortical connections are associated with sensorimotor deficits in children with congenital hemiplegia. *Brain Struct Funct* 2013; http://dx.doi.org/10.1007/s00429-013-0656-x [E-pub ahead of print]
8. Cioni G, Sales B, Paolicelli PB, Petacchi E, Scusa MF, Canapicchi R. MRI and clinical characteristics of children with hemiplegic cerebral palsy. *Neuropediatrics* 1999; **30**: 249–55.
9. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. *Neuroimage* 2000; **11**: 805–21.
10. Lee JD, Park HJ, Park ES, et al. Motor pathway injury in patients with periventricular leucomalacia and spastic diplegia. *Brain* 2011; **134**: 1199–210.
11. Patenaude B, Smith SM, Kennedy DN, Jenkinson M. A Bayesian model of shape and appearance for subcortical brain segmentation. *Neuroimage* 2011; **56**: 907–22.
12. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 2002; **33**: 341–55.
13. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997; **39**: 214–23.
14. Eliasson AC, Krumlinde-Sundholm L, Rosblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev Med Child Neurol* 2006; **48**: 549–54.
15. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *NeuroImage* 2012; **62**: 782–90.
16. Smith SM, Nichols TE. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage* 2009; **44**: 83–98.
17. Karsch K, Grinstead B, He Q, Duan Y. Web based brain volume calculation for magnetic resonance images. *Eng Med Biol Soc* 2008; 1210–3.
18. Scheck SM, Boyd RN, Rose SE. New insights into the pathology of white matter tracts in cerebral palsy from diffusion magnetic resonance imaging: a systematic review. *Dev Med Child Neurol* 2012; **54**: 684–96.
19. Hagmann P, Cammoun L, Gigandet X, et al. Mapping the structural core of human cerebral cortex. *PLoS Biol* 2008; **6**: e159.
20. Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Arch Gen Psychiatry* 2000; **57**: 449–56.
21. Janssen J, Aleman-Gomez Y, Reig S, et al. Regional specificity of thalamic volume deficits in male adolescents with early-onset psychosis. *Br J Psychiatry* 2012; **200**: 30–6.