Basal ganglia and thalamic volumes with motor and cognitive outcomes in very preterm 7 year old children.

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Target Audience: Scientists and clinicians interested in MRI applications and/or paediatric research.

Background & Aims: There are many long-term consequences of prematurity, including motor and cognitive impairments.[1] The basal ganglia and thalamus (BGT) are key relay nuclei within the brain that have been shown to play critical roles in normal motor and cognitive functioning.[2] Therefore, the aims of this study were to: 1) compare BGT volumes between very preterm (VP, born <30 weeks' gestation and/or <1250g birth weight) and term (born ≥37 weeks' gestation) children, and 2) evaluate the association between BGT volumes and motor and cognitive outcomes in VP children, at age 7 years.

Methods: *Participants:* This study included 154 VP and 36 term children at age 7 years. *Scanning techniques:* T_1 weighted images were acquired using a 3T Siemens Magnetom Trio MRI machine with the following parameters: TR=1900ms, TE=2.27ms, Flip angle=9°, FOV=210x210mm, Matrix=256x256, 0.8mm^3 isotropic voxels. *Image pre-processing:* All T_1 images were aligned to the anterior commissure and posterior commissure axis using 3D Slicer v4.1.1 (www.slicer.org). Brain extraction of the T_1 images was done using the FSL v.5.0.6 brain extraction tool (www.fmrib.ox.ac.uk/fsl). *BGT segmentation:* A normative paediatric template of the cohort was generated from 40 (20 VP and 20 term children) T_1 images using the Advanced Normalisation Tools (ANTs) template building tool (http://stnava.github.io/ANTs). Manual segmentation of the BGT (accumbens, caudate, pallidum, putamen and thalamus in both hemispheres) was performed on T_1 images of the same 40 subjects. A BGT tissue prior atlas was constructed by registering each of the 40 subjects' manual segmentations to the paediatric template space and averaging them across the 40 individuals. For BGT segmentation of the whole cohort (Fig. 1), the constructed BGT tissue priors were registered to each subject's T_1 image and segmentation was performed in native space using the SPM v.8 segmentation tool (http://www.fil.ion.ucl.ac.uk/spm). *Statistical analysis:* All statistical analyses were performed using linear regression. Comparison of BGT volumes between groups were adjusted for age at MRI and intracranial volume (ICV). Relationships between BGT volumes and motor outcome (Movement Assessment Battery for Children v.2, MABC) and IQ (Wechsler Abbreviated Scale of Intelligence, WASI) within the VP group were adjusted for age at testing and ICV.

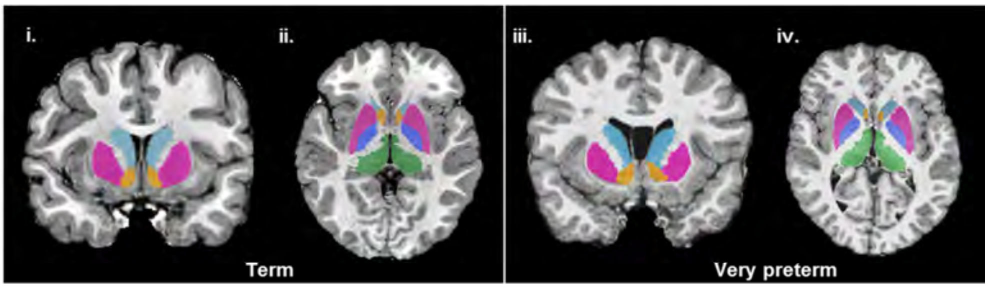

Fig. 1. Basal ganglia and thalamus segmentation for a term and very preterm subject in coronal (i,iii) and axial (ii,iv) views. Accumbens: *gold*, caudate: *light blue*, pallidum: *dark blue*, putamen: *pink*, thalamus: *green*.

Table 1. Comparison of BGT volumes in VP children compared with term children at age 7 years. (β=regression coefficient representing the percentage mean volume difference between birth groups; CI=confidence interval)

	Mean Volume (SD), mm^3		Mean Difference (%)	
	VP	Term	β (95% CI)	p
Left Accumbens	430.4(75.3)	467.2(84.4)	-0.61 (-5.81,4.58)	0.82
Left Caudate	3841.1(508.6)	4136.5(471.2)	-1.95 (-5.55,1.64)	0.29
Left Pallidum	1663.3(187.1)	1818.0(217.9)	-4.60 (-8.03,-1.18)	<0.01
Left Putamen	5452.0(575.2)	5693.2(537.2)	0.11 (-2.78,3.00)	0.94
Left Thalamus	7103.7(679.7)	7811.0(603.5)	-4.92 (-7.28,-2.57)	<0.01
Right Accumbens	477.2(78.3)	509.9(88.9)	0.19 (-4.90,5.28)	0.94
Right Caudate	3963.8(516.3)	4272.3(472.5)	-2.34 (-5.82,1.14)	0.19
Right Pallidum	1582.1(177.9)	1714.1(185.0)	-3.68 (-7.03,-0.32)	0.03
Right Putamen	5393.8(542.5)	5643.0(534.9)	-0.83 (-4.03,2.36)	0.61
Right Thalamus	7142.9(714.9)	7924.6(590.1)	-6.03 (-8.48,-3.58)	<0.01

Table 2. Associations between BGT volumes and motor and IQ measures in VP children at age 7 years. (β=regression coefficient representing the increase in outcome score per 1% increase in mean VP volume for each BGT structure; CI=confidence interval)

	MABC (Standard Score)		WASI (Full IQ)	
	β (95% CI)	p	β (95% CI)	p
Left Accumbens	0.05 (0.01,0.09)	0.02	0.16 (0.02,0.30)	0.03
Left Caudate	0.05 (0.01,0.09)	0.03	0.15 (-0.03,0.34)	0.11
Left Pallidum	0.08 (0.03,0.13)	<0.01	0.07 (-0.15,0.29)	0.55
Left Putamen	0.03 (-0.03,0.10)	0.27	0.16 (-0.08,0.40)	0.18
Left Thalamus	0.09 (0.03,0.15)	<0.01	0.07 (-0.24,0.38)	0.64
Right Accumbens	0.03 (-0.01,0.07)	0.10	0.28 (0.14,0.41)	<0.01
Right Caudate	0.07 (0.02,0.11)	<0.01	0.18 (-0.01,0.36)	0.06
Right Pallidum	0.08 (0.04,0.13)	<0.01	0.10 (-0.12,0.31)	0.37
Right Putamen	0.03 (-0.03,0.09)	0.35	0.13 (-0.12,0.39)	0.30
Right Thalamus	0.08 (0.02,0.14)	<0.01	0.003 (-0.25,0.26)	0.98

Results: There was evidence for bilaterally smaller pallidal and thalamic volumes in the VP group compared with term children (Table 1). Larger BGT volumes in VP children were associated with higher motor scores in all structures except the putamen (bilateral) and right accumbens (Table 2). Additionally, larger volume in the accumbens (bilateral) was associated with higher IQ in VP children (Table 2).

Discussion & Conclusions: VP children have reduced pallidal and thalamic volumes in both hemispheres compared with term children. Furthermore, there was strong evidence that larger BGT volumes (all structures except putamen and right accumbens) were associated with better motor functioning. There was also evidence that larger volume in the accumbens was associated with higher IQ. This study provides novel insights into the underlying neurological mechanisms for motor and cognitive deficits observed in VP children at age 7 years.

References

1 Anderson, P J & Doyle, L W. Cognitive and educational deficits in children born extremely preterm. *Seminars in Perinatology* **32**, 51-58 (2008).

2 Haber, S N. The primate basal ganglia: Parallel and integrative networks. *Journal of Chemical Neuroanatomy* **26**, 317-330 (2003).