DETERMINING THE MOST CONSISTENT METHOD FOR MRI HIPPOCAMPAL VOLUMETRY IN INFANTS AT TERM

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Introduction: The hippocampus is important in learning and memory functions, which are known to be impaired in preterm infants[1]. Furthermore, postnatal glucocorticoids, such as dexamethasone have been specifically associated with neurotoxic effects upon the hippocampus[2]. Magnetic Resonance imaging (MRI) is a sensitive technique that can assess the hippocampus, although this is more challenging in the unmyelinated newborn infant brain. The aims of this study were to utilize 3D MR imaging to determine the most reliable and consistent method for measuring hippocampal volumes in full term and preterm infants at term equivalent, and to compare hippocampal hemispheric asymmetry within different groups of infants.

Methods: Fifty-eight preterm and 22 full term control infants were included in the study. All infants were scanned at term equivalent in a 1.5T GE scanner with two imaging modalities: 3-D T1 spoiled gradient recalled (SPGR) (1.2mm coronal slices; flip angle 45°; Repetition Time (TR) 35ms; Echo Time (TE) 9ms; Field of View (FOV) 21 x 15cm; matrix 256 x 192) and T2 dual echo fast recovery fast spin echo sequences with interleaved acquisition (2mm coronal; TR 4000msec; TE 60 / 160msec; FOV 22 x 16cm; matrix 256 x 192, interpolated 512 x 512). Five randomly chosen infants were segmented twice each for five different methods of post-acquisition image processing:

1. t2w image registered to T1 image using multi-information non-linear registration.
2. raw t2w image.
3. volume math addition of raw t2w and pdw image (t2w+pdw).
4. t2w+pdw manually rotated and translated in the axial plane to be perpendicular to the fimbria of the long axis of the left hippocampus as visualized in sagittal view.
5. t2w+pdw manually rotated and translated into midline orientation, along the inter-hemispheric fissure in mid-sagittal plane, through the anterior commissure and posterior commissure (AC-PC) line in the axial plane, and passing through the PC in the coronal plane.

Intraclass correlation coefficients were calculated in order to determine the most reliable segmentation procedure. Tracing proceeded from the hippocampal tail to the head, according to previously defined anatomical criteria[3]. Each pair of hippocampi were traced twice, on both the original and mirrored image to eliminate hemispheric bias in the operator, and then averaged. Left and right hippocampal volumes were compared with a paired samples t-test for the whole cohort, as well as full term infants, preterm infants, and preterm infants separated on the basis of whether or not they had been exposed to postnatal steroids.

Results: Table 1 reveals that using raw images (t2w raw) on repeated volumetric measurements gave the most highly correlated results, and was therefore more reliable than using registered data. Adding together the t2w and pdw images (t2w+pdw) proved a more reliable method for hippocampal segmentation than using t2w alone (t2w raw). There was no improvement in reliability when re-orienting the images either midline (t2w+pdw midline) or perpendicular to the long axis of the hippocampus (t2w+pdw perp). Thus, the most reliable approach to measuring hippocampal volume in the newborn infant brain was the method where raw t2w and pdw volumes were added together in their original space. This was the best technique for both the right (99%) and left (96%) hippocampal volumes.

Table 1. Mean hippocampal volumes of five subjects segmented twice, plus intraclass correlation coefficients for five different methods of hippocampal segmentation.

	Right Hippocampus Volume		Left Hippocampus Volume	
	Mean (SD), ml	Intraclass Correlation	Mean (SD), ml	Intraclass Correlation
1. T2w Registered	1.10 (0.18)	0.83	1.09 (0.13)	0.55
2. T2w Raw	1.12 (0.17)	0.95	1.11 (0.17)	0.93
3. T2w+pdw Original	1.07 (0.21)	0.99	1.09 (0.20)	0.96
4. T2w+pdw Perp	1.21 (0.18)	0.96	1.19 (0.19)	0.28
5. T2w+pdw Midline	1.13 (0.14)	0.96	1.11 (0.14)	0.90

There was a significant difference observed between the size of the left and right hippocampal volumes when all infants were analyzed ($p<0.005$). All groups analyzed had significantly larger right hippocampal volumes in comparison to left hippocampi, except the preterm infants who had received postnatal steroids. (Table 2).

Table 2. Comparison of mean left and right hippocampal volume differences for the groups of infants analyzed.

		Mean Volume (SD), ml				
	n	**Right**	**Left**	Mean diff (ml)	95% CI of diff (ml)	Sig
Whole cohort	80	1.07 (0.15)	1.05 (0.16)	0.02	0.01, 0.03	p<0.005
Term Infants	22	1.19 (0.09)	1.16 (0.11)	0.03	0.01, 0.06	p= 0.007
All Preterm Infants	58	1.02 (0.14)	1.00 (0.15)	0.02	0.00, 0.03	p= 0.006
Preterm infants – PNS	18	0.98 (0.15)	0.98 (0.16)	0.00	-0.01, 0.02	p= 0.6
Preterm infants – No PNS	40	1.04 (0.13)	1.02 (0.15)	0.02	0.01, 0.03	p= 0.005

Conclusions:

1. The most reliable hippocampal segmentation for pediatric brain images was the method whereby the raw t2w and pdw volumes were added together without linear transformation or alteration in spatial orientation. The registered image was likely degraded due to interpolation, which negated any positive effect due to reduced image slice thickness. The combined raw pdw and t2w image revealed greater resolution for determining hippocampal boundaries than the raw t2w image alone in the unmyelinated newborn brain. Linear re-formatting of the images either midline or perpendicular may also have led to degradation of the image through interpolation, producing less reliable volumetric measures.
2. Right hippocampal volumes were significantly larger than the left for all infants except those who had received dexamethasone. We can infer that hippocampal asymmetry is normal and present as early as term equivalent in both genders. Dexamethasone exposure and/or illness in the preterm infant is causing loss of the normal hemispheric asymmetry which may be one of the mediators of adverse neurodevelopmental outcomes associated with steroid use in these infants.

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