Comparison of volumes of cerebellar lobules on structural MRI using manual and automatic segmentation in normal and alcohol-exposed children

Priya Lakshmi Narayanan[1,2], Christopher Warton[1], Sandra W Jacobson[3,4], Joseph L Jacobson[3,4], Christopher D Molteno[4], and Ernesta M Meintjes[1,2]
[1]Human Biology, University of Cape Town, Cape Town, South Africa, [2]MRC/UCT Medical Imaging Research Unit, Cape Town, South Africa, [3]Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, [4]Department of Psychiatry, University of Cape Town

Introduction: Fetal alcohol syndrome (FAS), the most severe of the fetal alcohol spectrum disorders (FASD), is caused by chronic heavy maternal alcohol consumption during pregnancy and estimated to be the most common preventable cause of learning disability worldwide [1]. MRI studies of children and adults with FASD have demonstrated disproportionately smaller cerebellum, parietal lobe, caudate nucleus, and corpus callosum [2]. Recent studies have reported a remarkably consistent deficit in alcohol exposed children in short delay classical eyeblink conditioning [3,4], which is known to be cerebellar dependent. Few automated methods are available for volumetric analyses of cerebellar lobules. To date, assessments of the cerebellum have not been validated using individual brain atlases in statistical parametric mapping (IBASPM). In this study, we compare volumes of individual cerebellar lobules in control children and children with FAS/partial FAS (PFAS) using manual delineation by an expert neuroanatomist and automatic segmentation using IBASPM (http://www.thomaskoenig.ch/Lester/ibaspm.htm) [5]. The results were examined for accuracy and consistency between automated and manual measures, and construct validity was assessed by investigating group differences between control and FASD subjects in automated and manual measures.

Methods: High-resolution anatomical T1-weighted three-dimensional (3D) structural images were acquired in 23 children with mean age 11.8±1.2 (range 9.7-13.7) using a 3T Allegra (Siemens, Erlangen, Germany) MRI scanner. These children (13 controls, 10 FAS/PFAS) who had been diagnosed for these disorders by three expert dysmorphologists [4], were scanned in the sagittal plane using a magnetization prepared rapid gradient echo (MPRAGE) sequence with parameters: TR = 2300 ms, TE = 3.93 ms, TI = 1100 ms, 160 slices, flip angle = 12 degrees, voxel size = 1.3×1.0×1.0 mm^3, scan time = 6.03minutes. The images were reoriented along the anterior posterior commisure (AC-PC) line horizontally and in the mid sagittal plane. For manual segmentation, images were resampled to isotropic 1 mm^3 voxels using Brain Voyager. The lobules were manually traced using Multitracer [6] software (http://www.loni.ucla.edu/Software/MultiTracer) by a neuroanatomist who was blinded to diagnosis. The tracings were performed in the sagittal plane using markings placed in the axial and coronal views to guide boundary determination. Boundaries were drawn on four times magnification to allow sub-voxel precision and reliable tracing of small-scale features. A three-dimensional binary mask image was reconstructed from the tracings, and volumes were determined for all of the cerebellar sub-regions. Ten subjects were randomly selected and traced again at a later stage to assess intra-rater reliability. The intra-class correlation coefficient (ICC) was 0.958. For automatic segmentation, IBASPM was used to automatically label the cerebellum based on the automated anatomical labeling (AAL) atlas [7] of 116 predefined segmented structures. The images were normalised and registered to the international consortium of brain mapping (ICBM) 152 template and the spatial transformation matrix computed. Using this matrix, the gray matter was transformed to the template space. Registered images were segmented into gray matter, white matter and cerebral spinal fluid in native space. Each gray matter voxel was labelled based on the AAL atlas, and an individual atlas was generated for each subject. The individual atlases were transformed to the native space using the inverse transformation matrix obtained during the segmentation and normalisation processes. The lobular volumes obtained using both methods are expressed in cubic centimeters.

Results: Table 1 shows a comparison of cerebellar lobular volumes in control and FAS/PFAS children determined using manual tracing and IBASPM for left and right hemispheres, respectively. Significant volume differences between the control and FAS/PFAS (p<0.001) children were observed in lobules I-V for both the right and left hemispheres for volumes measured manually, but this sub-region did not show any significant difference in the automatic measures. Except for cerebellar lobule VI, for which volumes measured manually were slightly larger in alcohol-exposed children, all regions were smaller in FAS/PFAS subjects compared to controls in both hemispheres. This increased volume in lobule VI is not observed in the automatic segmentation. Figure 1 shows a Bland-Altman difference plot comparing manual and automatic volume measures. The confidence bands (CB) represent 95% agreement between the methods. Some measures can be seen to exceed 2 standard deviations of the mean. The negative mean difference, indicated by the solid black line, ensures that the automated segmentation typically underestimates the volume compared to manual measures.

Table 1. Volumes of cerebellar lobules (Left and Right hemispheres) using manual tracing and automatic segmentation (IBASPM) for control children and children with FAS/PFAS

		LEFT Cerebellar Volumes (cm^3, mean ± SD)			RIGHT Cerebellar Volumes (cm^3, mean ± SD)		
Method	**Lobule**	**Control**	**FAS/PFAS**	**t**	**Control**	**FAS/PFAS**	**t**
Manual	I-V	6.8±1.2	4.6±1.3	4.2**	6.4±1.2	4.5±1.1	3.8**
	VI	7.4±1.4	8.5±1.9	-1.5†	7.5±1.1	8.2±2.0	-1.1
	Crus I	12.6±1.1	11.2±2.3	1.9†	12.4±1.5	11.2±2.7	1.2
	Crus II	9.7±1.2	8.4±1.9	2.0†	10.1±1.8	8.7±2.8	1.3
	VI I	4.1±0.9	3.3±0.8	2.3†	3.6±0.7	3.1±0.8	1.5†
	VIII	7.3±1.1	7.0±1.6	0.6	7.8±1.0	6.3±1.6	2.7*
	IX	4.9±0.9	4.0±1.1	2.0†	4.5±0.8	3.7±1.0	2.2†
	X	0.5±0.1	0.4±0.2	1.7†	0.5±0.1	0.4±0.2	1.5†
IBASPM	I-V	5.5±1.9	4.6±1.1	1.4†	4.7±0.9	3.9±1.0	1.8†
	VI	8.2±3.0	6.0±1.5	2.2†	8.5±3.0	6.3±1.4	2.3†
	Crus I	10.9±2.0	7.9±3.2	2.5†	10.7±2.3	7.9±2.7	2.7*
	Crus II	7.3±2.0	5.6±2.1	2.0†	7.5±1.7	5.6±2.0	2.4†
	VI I	2.0±0.6	1.6±0.6	1.6†	1.9±0.5	1.4±0.5	2.2†
	VIII	6.8±1.1	5.3±2.2	2.0†	8.4±0.9	6.3±2.5	2.5†
	IX	3.3±0.5	2.7±1.0	1.8†	3.1±0.4	2.5±0.9	2.1†
	X	0.3±0.1	0.2±0.1	1.7†	0.4±0.2	0.2±0.1	2.1†

(†$p \leq .10$ *$p < .01$ **$p < .001$)

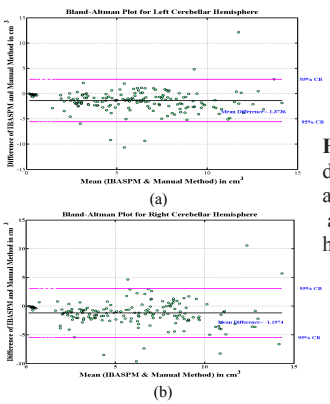

Figure 1. Bland Altman difference plot for manual and automatic segmentation.
a. Left hemisphere , b. Right hemisphere.

Conclusions: In this work, cerebellar lobular volumes obtained using manual tracing and IBASPM automatic segmentation was compared. Both left and right cerebellar lobules I to V by manual tracing are significantly (p<0.001) smaller in children with FAS/PFAS compared to control children. While these differences are also present in the automatic method, they are not statistically significant. The only region that is significantly smaller in alcohol-exposed children for the automated measures is right Crus I. Automated segmentation typically underestimates the volume compared to manual measures. This work demonstrates the need for improved automated segmentation tools for the cerebellum.

Acknowledgments
The South African Research Chairs Initiative of the Department of Science and Technology and National Research Foundation of South Africa, Medical Research Council of South Africa, NIH grants R03 TW007030, R01 AA016781; South African NRF Focus Area Grant FA2005040800024; Children's Bridge grant from the Office of the President of Wayne State University (WSU); Joseph Young, Sr., Fund from the State of Michigan; Siemens Medical Solutions South Africa.

References
1. Manning MA. et al., *Neurosci Biobehav Rev,* 2007;31(2): 230-8. 2. Jacobson JL. et al., *J Pediatr.* 1994;124: 757–764. 3. Jacobson SW. et al., *Alcohol. Clin. Exp. Res.,*2008;32(2): 365-372. 4. Jacobson SW. et al., *Alcohol. Clin. Exp. Res.,*2011; 35(2): 250-264. 5. Alemán G.et al., *NeuroImage,* 2006; 27(1).
6. Woods R et al., *NeuroImage* 2003; 19(4): 1829-1834. 7. Tzourio-Mazoyer N et al., *NeuroImage,* 2002; 15 (1): 273–289.