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# Quantification of total fetal brain volume using 3D MR imaging data acquired *in utero.*

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**ABSTRACT**

OBJECTIVE: Interpretation of MR imaging of the fetal brain *in utero* is primarily undertaken using 2D images to provide anatomical information about structural abnormalities. It is now possible to obtain 3D image acquisitions that allow measurement of fetal brain volumes that are potentially useful clinically. The aim of our current work is to provide reference values of total brain volumes obtained from a cohort of low risk fetuses with no abnormalities on ante-natal ultrasonography and *in utero* MR imaging.

METHOD: Images from volume MR acquisitions of 132 fetuses were used to extract brain volumes by manual segmentation. Reproducibility and reliability were assessed by analysis of the results of two subgroups who had repeated measurements made by the primary and a secondary observer.

RESULTS: Intra- and inter-observer agreement was high with no statistically significant differences between and within observers ($p= 0.476$ and $p= 0.427$, respectively). The results of the brain volume assessments are presented graphically with mean and 95% prediction limits alongside estimates of normal growth rates.

CONCLUSION: We have shown that fetal brain volumes can be reliably extracted from iuMR imaging 3D datasets with a high degree of reproducibility. The resultant data could potentially be used as a reference tool in the clinical setting.

- Measurement of fetal brain volume from iuMR imaging is a relatively new area of investigation and has been derived from motion corrected ultrafast 2D imaging but there is limited published data due to small sample sizes.
- Fetal brain volumes can be derived from 3D iuMR acquisitions with a high degree of reproducibility using freehand segmentation.
- Our work demonstrated a quadratic model provided best fit to describe the changes of fetal brain growth in relation to gestational age, increasing from a Mean value of 22.5 $cm^3$ to 274.7$cm^3$ between 18 and 36 weeks gestation.

Introduction

A routine part of prenatal assessment of the fetus is to monitor fetal growth and this is currently undertaken by ultrasonography (USS). Significant deviation from normal development has the potential to influence clinical management and, as such, it is important to establish reliable normal ranges. With regard to the central nervous system, indirect indicators of fetal brain growth are used routinely by measurement of skull dimensions e.g. biparietal diameter (BPD), occipito-frontal diameter and/or head circumference; although there are many cases when abnormal skull size is matched by abnormal brain size the correlation is not perfect. This is recognised in the neuropathology literature which uses the term microcephaly to indicate a small head size and micrencephaly to indicate a disproportionally small brain size in comparison to head size. While fetal biometry is an important part of prenatal screening to assess brain development there may be a disparity between those measurements and brain volume. Quantification of fetal brain volume using USS is possible (1) but not routinely used in clinical practice .

MR methods of estimating brain volumes in the fetus have previously focused on post processing ultrafast 2D MR acquisitions using bespoke software techniques. This has enabled quantification of fetal brain volume by semi or fully automated methods. Data regarding fetal supratentorial brain, cerebellum and midbrain structures have been published (2-4) as have exploration of changes in volume in the presence of pathology such as ventriculomegaly and posterior fossa abnormalities (5-7). The use of *in utero* Magnetic Resonance (*iu*MR) imaging 3D datasets to estimate brain volumes is a relatively new area of investigation.

Our work focuses on developing methods to acquire a volume dataset of the whole fetal brain using a 3D MR acquisition to provide anatomical detail for clinical assessment and for post processing to generate quantitative data of the imaged anatomy within clinically relevant timescales. Using these methods we aim to generate reference values of fetal brain volumes derived from a cohort of normally developing fetuses across a wide gestational age range.

**Methods**

*Participants*

Pregnant women whose fetuses had no abnormalities (brain or somatic) on USS and were at no increased risk of brain abnormalities were recruited from two sources; either as part of the extension to the MERIDIAN study (The Lancet (in press)) or through other research studies sponsored by our Institution. All women provided written informed consent with the

approval of the relevant Ethics Board. The gestational age at which the *iu*MR study was performed is quoted in relation to the estimate of fetal age made on second trimester USS. The *iu*MR studies were reviewed by a consultant pediatric neuroradiologist (PDG) with over 15 years' of experience reporting *iu*MR brain imaging in order to confirm normal appearances.

*Data Acquisition*

Our technique for acquiring and processing MR data of fetal brains *in utero* has been reported in detail elsewhere (8) but is summarised here and in table 1. All MR studies were performed on a 1.5T whole body scanner (HDx, GE Healthcare, Milwaukee) with an 8 channel cardiac coil positioned over the maternal abdomen either in the supine or lateral position. Maternal sedation was not used and the iuMR studies of the fetal brain were limited to 30 minutes table occupancy time. Our standard clinical 2D iuMR imaging protocol was used to acquire images in all three orthogonal planes. 3D data sets were acquired in the axial plane, relative to the fetal brain, using a balanced steady-state imaging sequence i.e. Fast Imaging Employing Steady-state Imaging (FIESTA, GE Healthcare, Milwaukee). This short (18-22seconds) imaging sequence allows acquisition of the entire fetal brain during maternal suspended respiration.

*Image processing and analysis*

The 3D datasets were anonymised and transferred to a standard PC where they were loaded into the public domain '3D Slicer' software (www.slicer.org). Anatomical areas of the fetal brain were outlined freehand on the axial images due to the higher in-plane resolution, although the coronal and sagittal planes were used for reference to improve accuracy (figure 1). The anatomical boundaries of five regions were delineated: cerebral ventricles, right and left cerebral hemispheres, infratentorial brain (cerebellum and brain stem to the level of the medulla/spinal cord junction) and the extra-axial CSF spaces with each area denoted by a different colour label (figure 1). We chose to segment the fetal brain by this method to aid future analysis of subdivisions but for the purpose of this work total brain volume (TBV) was calculated by adding the volumes of both cerebral hemispheres and the infratentorial structures (note these values do NOT include the volume of the enclosed cerebral ventricles). The resultant annotated areas were used to create 3D models of the fetal brain using the model-making algorithm within 3D Slicer, a requirement of the software in order for volume data to be ascertained (figure 5). Volumes were calculated by multiplying the number of voxels by the voxel size in each region of interest (ROI). The resultant volumes were used to chart fetal brain growth in relation to gestational age.

The manual segmentation of all cases was performed by a research MR radiographer with 8 years' experience of iuMR imaging (Observer 1, DJ) and a subgroup of 30 randomly selected cases were re-analysed by the same researcher after a 2 month interval blinded to the original measurements to investigate intra-observer reproducibility. A different group of 30 fetal brains were analysed by a second operator with one year of experience (observer 2, RA) to study inter-observer reliability.

*Statistical Analysis*

All total brain volumes were rounded to one decimal place and statistical analysis on the data performed using SPSS software version 20 (SPSS, Chicago, IL).

Intraclass correlation coefficient (ICC) was calculated to convey association within and between observers for fetal brain volumes and independent *t*-tests were used to compare differences. Bland-Altman plots were used to assess inter and intra observer agreement, variability and bias. Disagreement between measurements was considered clinically significant if differences in volume measurements both between and within raters were >10%.

Regression Analysis of fetal brain volumes versus gestational age was performed and regression fit chosen on the basis of highest adjusted $R^2$ value selected by successive analysis of polynomial fits (linear, quadratic and cubic). Analysis of the residuals was performed to check model fit and best regression fit used to determine 95% confidence intervals (CI) and prediction limits. 2 and 3 Standard deviations from the mean were calculated at each time point based on the original raw data which are presented in tabulated form.

**Results**

132 normal fetal brains were analysed between 18 and 36 weeks gestation.

The intra-rater analysis showed good repeatability of TBV measurements when observer 1 re-analysed a subgroup of 30 cases after a 2 month period (ICC=0.999, CI, 0.998-1.00, p<0.001). The one sample *t* test revealed that the brain volume differences between measurements were not statistically significant, $t(29)=0.805$, $p=0.427$, (95% CI -0.68 to 1.57). The Bland-Altman plot and the histogram of the differences between measurements are shown in Figure 3a and 3b with one value outside the 95% CI but no bias between measurements observed (B= -0.001, $p=0.877$). Table 2 shows the raw data TBV of first and second measurements and the percent difference between the two, which were between 0.31 and 7.10% (Mean 0.93%, SD 3.39%)

Inter-rater analysis demonstrated good reliability with no statistically significant difference found between measurements: $t(29)=0.722$, $p=0.476$ (95% CI, -1.799 to 3.761). The average measure ICC was 0.977, $p<0.001$ (95% CI, 0.952 to 0.989). The corresponding Bland-Altman plot for inter-rater agreement (Figure 4a) demonstrates the limits of agreement with one value outside the 95% CI and a bias toward higher values by the more experienced operator 1 (DJ) (B= -0.123, $p= 0.001$). The changes in measurement between observers as a percentage difference range between 0.05 and 9.31% (Mean 1.27%, SD 4.8%) as shown in Table 2a.

The TBV of the 132 fetuses are shown in Table 2b and presented graphically in Figure 2 which displays the lines for CI's and prediction limits for each gestational age determined by the best regression fit. This was found to be a quadratic model with $R^2_{adj}= 0.974$ whose prediction equation is $y=0.53x -13.33x+ ^{2}89.69$. TBV ranged from 20.2cm$^3$ at 18 weeks to 289.8cm$^3$ at 36 weeks gestation. Surface reconstructions of fetal brains at different gestations with the corresponding volume data are shown in figure 5.

*Discussion.*

We have shown that quantification of fetal TBV using 3D steady state sequences is possible in second and third trimester fetuses. The time required for manual segmentation ranged between 1 and 3 hours depending on the complexity of the surfaces (more mature fetuses have more complex surfaces because of progressing sulcation/gyration). Despite this time requirement, our method appears to be accessible, easily replicated and reproducible, even when undertaken by a relatively inexperienced operator. We present the results of 132 normal fetal brains in this paper but recognise that we require more cases to consolidate the data, particularly at the upper and lower ends of our range of gestational ages. Although the predicted values are more realistic they were calculated with small numbers e.g. 2 data points at 18 gestational weeks, and 3 at 19 gestational weeks which has resulted in lower range negative predictive values so should be taken with caution. It is possible therefore, the standard deviations calculated from the original TBV data may provide more reliable values for these gestations.

It is not possible to judge how accurate our estimates of TBV are, as we do not know the real volumes (or weights) of the brains assessed. This is a common problem for radiological studies and is frequently insurmountable. The only foreseeable way of resolving the problem

is to compare our volume measurements with brain weights measured post-mortem in cases where the pregnancy is terminated (utilising the well-defined density estimates of the fetal brain) (9) although the delay between iuMR study and the termination of pregnancy is a likely confounding factor. Alternatively, it may be possible to use our *iu*MR methods to estimate the volume of brain models of known volume that have similar complexity and size to fetal brains at different stages of gestation and this work is currently underway at our Institution.

In the absence of accuracy data we have to assess the reliability and reproducibility of our methods, specifically comparing the results of different observers and the results of the same observer at different times. This is important in order to ensure any deviation from values observed in the normal population can be assigned to abnormal development rather than inconsistencies in the methods used to extract the data. Our analysis by ICC and Bland-Altman plot have shown that the discrepancies both within the same rater and between raters were not statistically significant and are encouraging that there are not likely to be any major systematic methodological flaws. Inter-observer agreement was not as closely matched when compared with intra-observer assessments as shown by the wider limits of agreement and the bias toward higher volumes by the more experienced observer, but these differences are still small and not likely to cause clinically relevant errors.
The discrepancies could be due in part to earlier inexperienced measurements by the less experienced observer or due to variation in the practical aspects of annotation such as windowing the images.

One possible solution to the time taken for manual segmentation is to automate the process and several previous studies have described such methods to define anatomical areas of the fetal brain from 2D *iu*MR imaging data. Most have focused on different anatomical sub-divisions of the brain making it difficult to correlate our TBV findings with the published work, indeed most previous studies report volume data from the supratentorial brain only (10-12). Other studies have reported brainstem and cerebellar volumes but without the accompanying or paired supratentorial data (2, 6, 13). We chose to quantify the fetal TBV as defining the borders of the whole brain which can be easily identified due to the contrast between the brain paranchyma and CSF, whereas smaller areas within the brain are less consistently identified due to poor resolution (12).

Egana-Ugrinovic, Sanz-Cortes (14) did calculate TBV (i.e. supra and infratentorial compartments) for 50 fetuses at 37GW and reported mean values of 312.07 $cm^3$ (SD 40.85$cm^3$) that included intraventricular CSF spaces, unlike our data which measured brain parenchymal volume only. We cannot compare our data with that of Egana-Ugrinovic et al. directly because we do not have any data for 37GW fetuses (only to 36 weeks), although extrapolation of our curves does suggest a close match.
Even with the difference in anatomical areas measured previous studies report a growth rate of 15% per week (2, 7). Our work demonstrated a quadratic model provided best fit to describe the changes of fetal brain growth in relation to gestational age.

*Conclusion*

This study demonstrates a simple method to post process 3D iuMR data to determine quantitative measurements of the fetal brain with a high degree of reproducibility. The resultant graph of normal brain volumes across a broad range of gestations with associated prediction limits could potentially be used as a reference tool in the clinical setting. The normative data generated will allow comparisons to be made for the brain volumes of fetuses in whom there is suspected abnormal development. This additional information allows the possibility of building on the findings determined by routine imaging and biometry, providing additional or confirmatory evidence.

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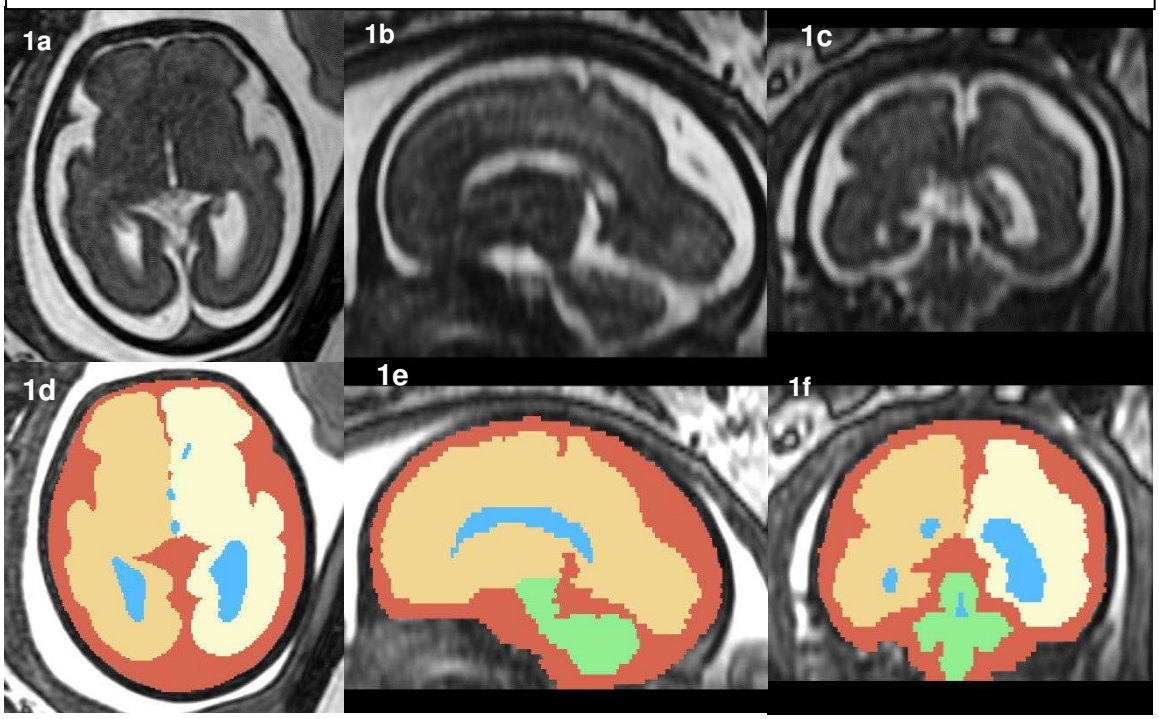
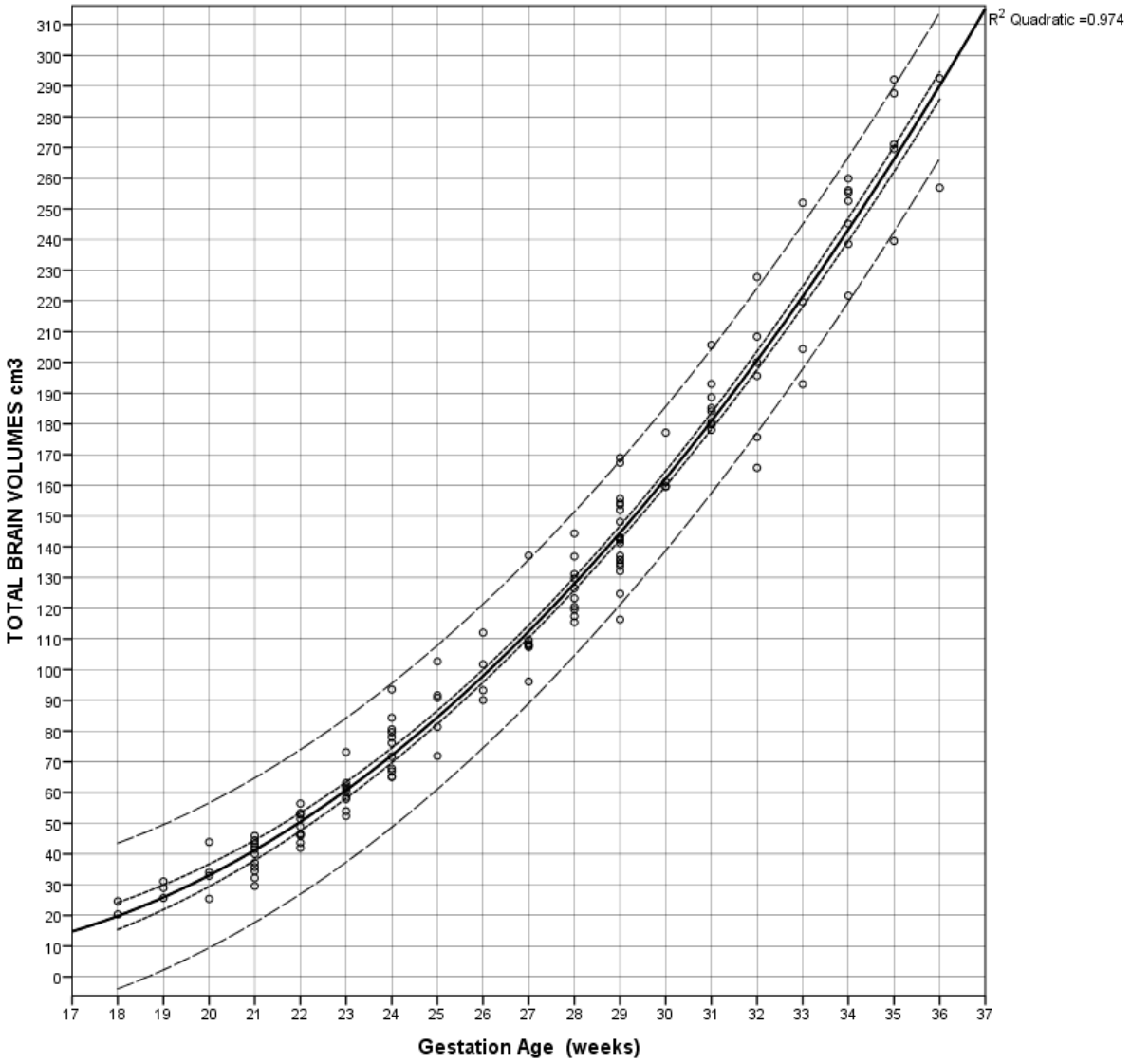
Figure 1. Axial image (1a) and reconstructed coronal and sagittal images as displayed by the 3D Slicer software. Figures 1d, 1e and 1f of the same images as above but with manual annotation completed and the different regions represented by different colours.



| Table 1. Parameters for Fetal iuMR Brain Imaging | | | | | | | |
|---|---|---|---|---|---|---|---|
| | T2 SSFSE | FIESTA | 3D FIESTA | DWI | FLAIR | T1 | MOVIE |
| Repetition Time | Minimum (2000) | Minimum (4.2) | Minimum (4.4) | 4000 | Minimum (2700) | Minimum (6.2) | 4.6 |
| Time to Echo | 120 | Minimum (2.2) | Minimum (2.4) | Minimum | 122 | Minimum (3.3) | 3 |
| Flip Angle | - | 70 | 60 | - | - | 45 | 45 |
| Bandwidth(KHz) | 62.5 | 100 | 125 | 250 | 41 | 31 | 166 |
| Inversion Time | - | - | - | - | 2000 | - | - |
| PREP TIME | - | - | - | - | - | 2000 | - |
| NEX | 1 | 1 | 0.75 | 4 | 0.5 | 1 | 1 |
| Slice Thickness/ Slice Gap (mm) | 4/0 | 4/0 | 2.0 - 2.6/0 | 4/0.5 | 4/0.4 | 4/0 | 18 |
| Field of View (Adjusted to patient) | 32x32 | 38x34 | 32x26 | 40x36 | 35x35 | 38 | 41 |
| Freq/ Phase Matrix | 256/256 | 384/256 | 320/256 | 128/128 | 256/192 | 192/128 | 192/256 |
| B Value | | | | 600-800 | | | - |
| Scan Time (Secs) | 32 | 25 | 21 | 64 | 54 | 51 | 30 |

Figure 2. Graphical Representation of Total Brain Volumes at each Completed Week. Dotted lines are Confidence Intervals and dashed lines Prediction Limits based on the Quadratic Regression Fit.



| **Table 3**. Total Brain Volumes | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gestation (Completed Weeks) | Frequency (n=132) | RANGE $cm^3$ | | Values Based on Original Raw Data ($cm^{3)}$ | | | | | | PREDICTION LIMITS using Polynomial Regression ($R^2$= 0.974) | | | | |
| | | Minimum | Maximum | Mean | SD | 3SD Below Mean | 2SD Below Mean | 2SD Above Mean | 3SD Above Mean | Predicted Mean Value | Lower Predicted CI | Upper Predicted CI | Lower predicted Limit | Upper predicted Limit |
| 18 | 2 | 20.3 | 24.6 | 22.5 | 2.1 | 16.1 | 18.2 | 26.7 | 28.8 | 19.8 | 12.6 | 27.0 | -4.6 | 44.2 |
| 19 | 3 | 25.7 | 31.1 | 28.6 | 2.7 | 20.4 | 23.1 | 34.0 | 36.7 | 25.9 | 20.2 | 31.6 | 1.9 | 49.9 |
| 20 | 4 | 25.4 | 44.2 | 34.1 | 7.6 | 11.3 | 18.9 | 49.3 | 56.9 | 33.0 | 28.5 | 37.5 | 9.3 | 56.8 |
| 21 | 11 | 29.6 | 45.9 | 38.8 | 5.4 | 22.7 | 28.1 | 49.5 | 54.8 | 41.2 | 37.7 | 44.8 | 17.6 | 64.8 |
| 22 | 10 | 42.0 | 56.4 | 48.7 | 4.6 | 34.9 | 39.5 | 58.0 | 62.6 | 50.5 | 47.5 | 53.4 | 27.0 | 74.0 |
| 23 | 9 | 52.3 | 73.2 | 60.3 | 6.0 | 42.2 | 48.3 | 72.4 | 78.4 | 60.8 | 58.1 | 63.5 | 37.3 | 84.2 |
| 24 | 11 | 65.1 | 93.6 | 75.4 | 9.0 | 48.3 | 57.3 | 93.4 | 102.4 | 72.1 | 69.4 | 74.8 | 48.6 | 95.6 |
| 25 | 5 | 71.9 | 102.7 | 87.7 | 11.6 | 52.8 | 64.4 | 110.9 | 122.5 | 84.5 | 81.8 | 87.3 | 61.0 | 108.0 |
| 26 | 4 | 90.1 | 112.0 | 99.3 | 9.8 | 69.8 | 79.7 | 118.9 | 128.7 | 98.0 | 95.1 | 100.8 | 74.5 | 121.4 |
| 27 | 7 | 96.1 | 137.1 | 110.6 | 12.6 | 72.9 | 85.5 | 135.7 | 148.3 | 112.4 | 109.6 | 115.3 | 89.0 | 135.9 |
| 28 | 10 | 92.8 | 144.3 | 126.5 | 9.2 | 98.9 | 108.1 | 144.8 | 154.0 | 128.0 | 125.1 | 130.9 | 104.5 | 151.5 |
| 29 | 20 | 116.3 | 169.0 | 143.2 | 13.1 | 104.0 | 117.1 | 169.3 | 182.4 | 144.6 | 141.8 | 147.4 | 121.1 | 168.1 |
| 30 | 4 | 159.6 | 177.2 | 164.4 | 8.6 | 138.8 | 147.3 | 181.5 | 190.1 | 162.2 | 159.5 | 165.0 | 138.8 | 185.7 |
| 31 | 8 | 178.1 | 205.7 | 186.9 | 9.1 | 159.7 | 168.8 | 205.0 | 214.0 | 180.9 | 178.2 | 183.7 | 157.5 | 204.4 |
| 32 | 6 | 165.7 | 227.8 | 195.5 | 22.4 | 128.3 | 150.7 | 240.4 | 262.8 | 200.7 | 197.6 | 203.7 | 177.2 | 224.2 |
| 33 | 4 | 192.9 | 252.0 | 217.3 | 25.6 | 140.4 | 166.0 | 268.5 | 294.1 | 221.5 | 217.9 | 225.1 | 197.9 | 245.1 |
| 34 | 7 | 221.7 | 262.4 | 247.0 | 13.3 | 207.1 | 220.4 | 273.6 | 286.9 | 243.3 | 238.8 | 247.8 | 219.6 | 267.1 |
| 35 | 5 | 239.5 | 292.1 | 272.0 | 20.7 | 210.0 | 230.6 | 313.3 | 334.0 | 266.2 | 260.5 | 271.9 | 242.2 | 290.2 |
| 36 | 2 | 256.9 | 292.5 | 274.7 | 25.2 | 199.0 | 224.2 | 325.1 | 350.3 | 290.2 | 283.0 | 297.3 | 265.8 | 314.5 |

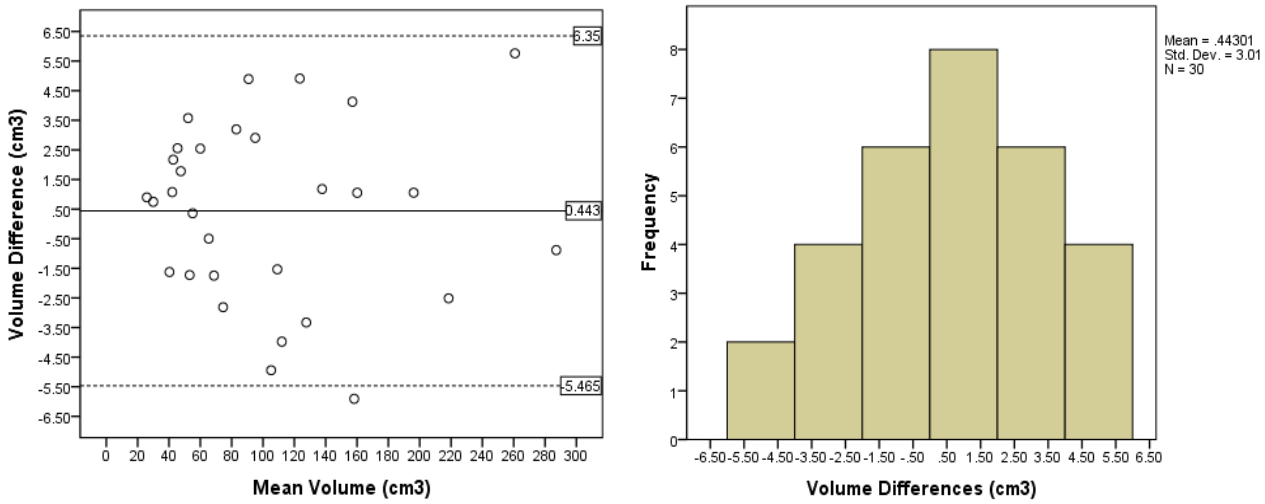



Figure 3. Bland Altman plot (left) of the differences between the two measurements made by the experienced operator (observer 1, DJ) Solid black line=mean. Dashed lines=95% limits of agreement. Right -Histogram of the frequencies of difference between intra-rater measurements.

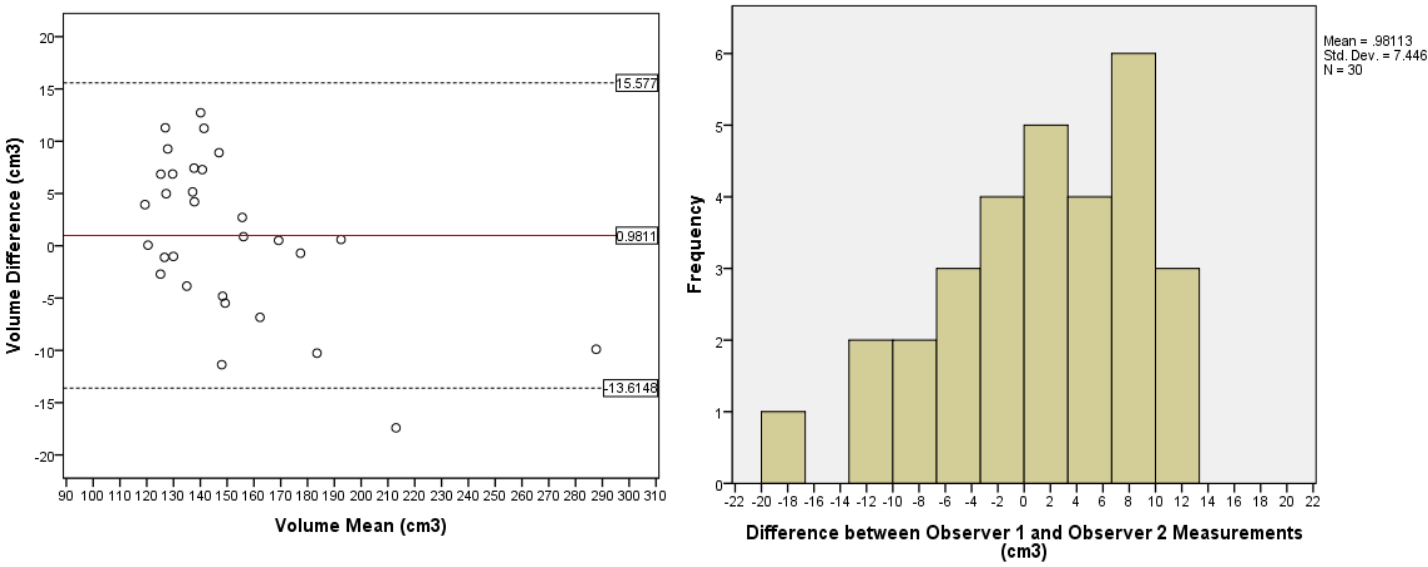



Figure 4. Bland-Altman plot of differences between operator 1 (DJ, experienced) and 2 (RA, newly trained). Solid black line=mean. Dashed lines=95% limits of agreement. Right -Histogram of the frequencies of difference between inter-rater measurements.

| Table 2a Intra Rater Reproducibility TBV Measurements | | | |
|---|---|---|---|
| | Observer 1 First Measurement | Observer 1 Second Measurement | % Change |
| 1 | 69.6 | 67.8 | -2.5 |
| 2 | 121.0 | 125.9 | 4.1 |
| 3 | 109.9 | 108.4 | -1.4 |
| 4 | 25.4 | 26.3 | 3.5 |
| 5 | 44.1 | 46.7 | 5.8 |
| 6 | 88.3 | 93.2 | 5.5 |
| 7 | 107.7 | 102.7 | -4.6 |
| 8 | 29.6 | 30.3 | 2.5 |
| 9 | 287.6 | 286.7 | -0.3 |
| 10 | 50.4 | 54.0 | 7.1 |
| 11 | 159.6 | 160.7 | 0.7 |
| 12 | 41.6 | 43.8 | 5.2 |
| 13 | 76.0 | 73.2 | -3.7 |
| 14 | 114.0 | 110.0 | -3.5 |
| 15 | 54.0 | 52.3 | -3.2 |
| 16 | 195.6 | 196.7 | 0.5 |
| 17 | 58.7 | 61.3 | 4.3 |
| 18 | 219.7 | 217.2 | -1.1 |
| 19 | 81.3 | 84.5 | 3.9 |
| 20 | 41.5 | 42.6 | 2.6 |
| 21 | 257.9 | 263.7 | 2.2 |
| 22 | 155.0 | 159.2 | 2.7 |
| 23 | 65.6 | 65.1 | -0.8 |
| 24 | 161.2 | 155.2 | -3.7 |
| 25 | 46.6 | 48.4 | 3.8 |
| 26 | 54.9 | 55.3 | 0.7 |
| 27 | 41.1 | 39.5 | -4.0 |
| 28 | 129.3 | 125.9 | -2.6 |
| 29 | 93.6 | 96.5 | 3.1 |
| 30 | 137.1 | 138.3 | 0.9 |

| Table 2b. Inter Rater Reproducibility TBV Measurements | | | |
|---|---|---|---|
| Case Number | Measured TBV Observer 1 | Measured TBV Observer 2 | % change |
| 31 | 134.5 | 139.7 | 3.8 |
| 32 | 120.4 | 120.5 | 0.1 |
| 33 | 153.7 | 142.3 | -7.4 |
| 34 | 117.4 | 121.3 | 3.4 |
| 35 | 135.7 | 139.9 | 3.1 |
| 36 | 123.2 | 132.5 | 7.5 |
| 37 | 133.7 | 146.5 | 9.5 |
| 38 | 137.1 | 144.4 | 5.3 |
| 39 | 152.0 | 146.5 | -3.6 |
| 40 | 188.7 | 178.4 | -5.4 |
| 41 | 192.2 | 192.8 | 0.3 |
| 42 | 121.3 | 132.6 | 9.3 |
| 43 | 168.9 | 169.5 | 0.3 |
| 44 | 142.5 | 151.4 | 6.2 |
| 45 | 155.7 | 156.5 | 0.6 |
| 46 | 135.7 | 147.0 | 8.3 |
| 47 | 136.9 | 133.0 | -2.8 |
| 48 | 177.7 | 177.0 | -0.4 |
| 49 | 154.3 | 157.0 | 1.8 |
| 50 | 124.8 | 129.7 | 4.0 |
| 51 | 165.7 | 158.9 | -4.1 |
| 52 | 221.7 | 204.3 | -7.9 |
| 53 | 292.6 | 282.7 | -3.4 |
| 54 | 127.2 | 126.1 | -0.9 |
| 55 | 130.4 | 129.4 | -0.8 |
| 56 | 133.9 | 141.4 | 5.5 |
| 57 | 121.8 | 128.7 | 5.6 |
| 58 | 126.5 | 123.8 | -2.1 |
| 59 | 126.2 | 133.1 | 5.4 |
| 60 | 150.7 | 145.9 | -3.2 |

Figure 5. 3D reconstructions of fetal brains with corresponding volume measurements at four different gestations.