

Morphometric human embryonic brain features according to developmental

stage

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Bulleterd statements

What is already known about this topic?

■ Comparing morphometric data based on embryonic stages and sonographic information can be valuable; however, classic embryology has provided relatively little morphometric data.

What does this study add?

33 ■ Linear, area, and volume measurements of the human embryonic brain
34 according to Carnegie stages were obtained using magnetic resonance
35 microscopy data.

36 ■ All linear measurements, except for bitemporal length (BT) and mesencephalic
37 height (MH), increased non-monotonically.

38 ■ A high correlation between BT and both whole-brain ($r = 0.98$) and
39 prosencephalon volume ($r = 0.99$) was found.

Abstract

Objectives: The present study investigated linear, area, and volume measurements of human brain samples according to Carnegie stages (CS) in an attempt to select suitable morphometric features that reflect embryonic development.

Methods: Using magnetic resonance (MR) imaging, we measured seven linear segments, three separate areas, and three regional volumes in 101 samples between CS 13 and CS 23. Brain volume was determined via manual segmentation of the MR image, whereby a formula was generated to estimate the volume of each linear measurement.

Results: All parameters correlated with crown-rump length. Bitemporal length (BT) and mesencephalic height increased linearly according to the CS, and a high correlation between BT and both whole-brain ($r = 0.98$) and prosencephalon volume ($r = 0.99$) was found when brain cavity volume was excluded.

Conclusion: Morphometric data related to human embryonic stages are valuable

for correcting and comparing sonographic data. The present approach may contribute to improvements in prenatal diagnostics by enabling the selection of more suitable measurements during early embryonic stages.

Key Words

human brain, human embryo, magnetic resonance imaging, length and area measurements

Abbreviations

Carnegie stage (CS), magnetic resonance (MR), fronto-occipital diameter (FO), bitemporal diameter (BT), mesencephalon length (ML), mesencephalon height (MH), cerebellar length (CL), cerebellar height (CH), biparietal diameter (BPD), crown-rump length (CRL).

Introduction

The use of ultrasound for prenatal diagnostics has rapidly increased over the past 25 years¹⁻⁹. The application of three-dimensional (3D) sonography with high-frequency transvaginal transducers has expanded and now fosters 3D sonoembryology, which provides a basis for assessing normal human development and can also be useful in detecting developmental anomalies. Thus, such technology could contribute to more accurate prenatal diagnoses, as well as enable a shift in the diagnostic time window (from the second to the first trimester). At present, an embryo at 7 gestational weeks (based on the last menstrual period) or younger, which corresponds to a Carnegie stage (CS) of 15–16, can be assessed using morphological and morphometrical analyses. While abnormal embryos younger than 10 weeks' gestation may be observed incidentally, systematic screening using sonographic parameters could result in the detection of abnormalities during the late, first trimester (10–11 weeks' gestation)¹.

87 The human brain develops in a very complicated manner during the
88 embryonic period¹⁰. For example, three brain vesicles that develop at the cranial
89 end of the neural tube differentiate to form the prosencephalon, mesencephalon,
90 and rhombencephalon at CS13¹¹. Moreover, the brain does not reach definitive
91 organization until after CS15, with the emergence of the telencephalon.

92 Application of sonoembryology to the embryonic period is essential for our
93 comprehension of brain development. Moreover, determining an appropriate
94 developmental stage in which sonography can be applied is important for
95 precise diagnostics¹². However, exact staging is still difficult because it requires
96 imaging internal structures of the brain at the microscopic level¹³.

97 Morphometrical studies (both two- and three-dimensional) can be
98 analyzed using serial histological sections and visualized via 3D modeling and
99 illustrations¹³⁻¹⁵. However, these methods are laborious and inaccurate.

100 Moreover, histological sections contain artefacts due to the use of fixative, which
101 can cause tissue shrinkage and deformation from dehydration¹⁶. Finally, very

few morphometric studies of the human embryonic brain have employed the

CS^{14,15}.

Recently, we analyzed morphogenetic and volumetric measurements of the embryonic brain via 3D reconstructions of MR microscopic data¹⁰, and observed dramatic growth at each CS. Thus, we used the same materials in our current study to measure linear segments and specific areas in MR images, similar to what has been reported in previous studies^{14,15}. One advantage of this approach is that we were able to accurately measure a suitable plane, allowing for the estimation of a correlation between linear and volumetric measurements (region-by-region) using staged embryos as early as CS13, which corresponds to 6weeks' gestation.

Materials and methods

Embryonic specimens

Approximately 44000 human embryos (comprising the Kyoto Collection) are stored at the Congenital Anomaly Research Center at Kyoto

University^{17,18}. In most cases, the pregnancies from which these embryos were derived were terminated during the first trimester for socioeconomic reasons under the Maternity Protection Law of Japan. From this collection, we measured, examined, and staged embryos using criteria provided by O’Rahilly and Müller¹¹. Approximately 1200 well-preserved human embryos were judged to be normal by two of the authors (C.U. and S.Y.) based on a gross examination. These embryos were later subjected to MR microscopic imaging; the conditions for which have been previously described elsewhere¹⁷⁻¹⁹.

In the present study, 101 samples from the CS13–CS23 range (nine or 10 samples for each stage, with the exception of CS13, for which there were five samples), and their associated morphometric analyses, were selected from the 1200 MR imaging datasets. The selected embryos were identical to those used in a previous study¹⁰.

Morphometric analysis

MR imaging datasets for each embryo were initially obtained as 256 ×

256 × 512 voxel data¹⁹. The midsagittal and transverse planes were used according to previous studies, with minor modifications^{14,15} (Figure 1). The planes for length and area measurements were digitally resectioned using OsiriX™ software (ver. 4.0, Pixmeo SARL, Geneva, Switzerland).

The following seven segments were measured, which were consistent with a previous study¹⁴: fronto-occipital diameters (FOa and FOb) and bitemporal diameter (BT) as substitutions for the prosencephalon, mesencephalon length (ML) and mesencephalon height (MH) as substitutions for the mesencephalon, and cerebellar length (CL) and cerebellar height (CH) as substitutions for the rhombencephalon and cerebellum, respectively (Figure 1A). Area measurements were obtained for three regions in the midsagittal section that corresponded to the prosencephalon, mesencephalon, and rhombencephalon¹⁵.

Brain volume was measured by manual segmentation, as described previously¹⁰. Briefly, brains and ventricles were segmented for 3D reconstruction using the FSL view of the FMRIB Software Library™ (ver. 4.1.9, Analysis Group,

FMRIB, Oxford, UK). Three-dimensional brain morphology was computationally reconstructed with AmiraTM software (ver. 5.4.0, Visage Imaging, Berlin, Germany).

Brain and whole embryo volumes were calculated using OsiriXTM software (ver. 4.0, Pixmeo SARL, Geneva, Switzerland). Vesicles were divided into three regions according to the following anatomical landmarks: the supramammillary recess and posterior commissure were used to define the prosencephalon and mesencephalon; the isthmic recess and the isthmic groove were used to define the mesencephalon and rhombencephalon; and the C1 vertebral level was used to define the separation between the rhombencephalon and spinal cord¹⁰. After dimensional matching, a formula was derived to estimate brain volume from the linear measurements. We then analyzed both total brain volume (with the ventricles) and brain volume without the ventricles, since an increase in ventricular volume – a feature of the embryonic period – could have influenced our measurements^{5,6,10,15}. The Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (E986) approved this study.

166

167 **Results**

168 ***Linear, area, and volume measurements***

169 **1. Linear measurements**

170 The seven length segments evaluated here were linearly correlated with
171 CRL (Table 1, Supplementary figure 1). The correlation coefficient was large for
172 all segments ($r \geq 0.91$), and the slopes of the regression lines were consistent
173 with those of a previous study (with the exception of the CL)¹⁴. In that prior study,
174 the correlation coefficients for CL and CH were small ($r = 0.14$ for CL and 0.52
175 for CH)¹⁴.

176 The seven length segments were plotted by CS group (Figure 2). BT and
177 MH exhibited a nearly linear increase, while other segments increased
178 non-monotonically during CS13 and CS23. A plateau phase between CS19 and
179 CS20 was observed in several segments (FOa, FOb, ML, and CL). It should be
180 noted that we were unable to compare our data with that of a previous study
181 because the segment and CS correlations in that study were not precisely

analyzed¹⁴.

2. Area measurements

Areas in the midsagittal section that corresponded to the whole brain, as well as the prosencephalon, mesencephalon, and rhombencephalon, were measured (Figure 3). Each area increased between CS13 and CS23. Exponential curves demonstrated a good fit to the data ($R^2 = 0.92\text{--}0.97$), except for the rhombencephalon area ($R^2 = 0.85$); this finding was consistent with that of a previous study (Table 2)¹⁵.

3. Volume measurements

When brain volume was measured without the ventricles (i.e., brain tissue only), we determined that it increased exponentially until CS23. On the other hand, when ventricular volume was included in the measurement, we determined that brain volume increased and then plateaued between CS19 and CS20 (Table 3).

Tissue volumes from the three brain vesicles grew exponentially, though the growth rates differed. Volumes including cavities did not grow exponentially. Rhombencephalon volume increased with a local maximum at CS19, which was affected by cavity growth; namely, the rhombencephalon brain cavity, which becomes the fourth ventricle, reached its maximum volume at CS19.

Large brain cavities, with non-exponential volume changes, are a prominent feature during the early embryonic period. Whole-brain cavity volumes were greater than whole-brain tissue volumes between CS14 and CS18 (Table 3). The ratio of whole-brain cavity to tissue volume reached a maximum at CS17 (ratio = 1.46), after which brain tissue volume became greater than brain cavity volume. The maximum brain cavity to brain tissue volume ratio was noted at CS17 in all three regions and was particularly prominent in the rhombencephalon (prosencephalon: 1.11, mesencephalon: 1.04, and rhombencephalon: 1.84).

Predicting brain volume from linear data and measurements

A formula was generated to estimate whole-brain volume both with and without ventricles, based on matched dimensions. These results are summarized in Table 4. A large correlation was observed with the linear BT measurement (total volume: $r = 0.97$, non-ventricular volume: $r = 0.98$). BT was also highly correlated with prosencephalon volume (total volume: $r = 0.98$, non-ventricular volume: $r = 0.99$). These correlations were larger than for any other measurement or combination. Other measurements, such as FOb and combinations (e.g., FOa*FOb*BT), were highly correlated with prosencephalon volume, both with and without inclusion of ventricular volume.

For the mesencephalon, all linear measurements examined (ML and MH) were highly correlated with mesencephalon volume, both with and without inclusion of ventricular volume. Correlations were also high for estimating the rhombencephalon ($r = 0.80$ for CH³, and 0.92 for CL³).

Discussion

The human embryonic brain develops in a complicated manner over a short period¹⁰, with growth speed and increases in measurements varying according to developmental stage. Thus, the determination of developmental stage is necessary for a more precise detection of embryonic abnormalities. Improvements in sonographic resolution may contribute to our ability to observe detailed and precise embryonic morphology. Nevertheless, it remains unclear how measurements, which reflect developmental features, relate to developmental stages. Classic embryology using histological techniques has revealed morphological features according to developmental stage, and this forms the current basis of sonoembryology. However, classic embryology has provided relatively little morphometric data^{14.15}. The present study improved upon previous methods by providing a suitable plane for a morphometric analysis from staged human embryos using MR microscopic data.

In the current study, the increases in brain cavity and whole body volume (in relation to the CRL) were comparable to those reported by Blaas' sonoembryologic study²⁰ (Figure 4). Regarding the prosencephalon, the volume

in both studies increased exponentially with overlapping values (Figure 4B). The volume of the mesencephalon was variable across samples, especially for larger specimens (CRL > 20 mm), and increased in a broadly linear manner. With respect to the rhombencephalon, the variance was considerable among smaller samples (CRL > 10 mm). The increasing growth rates of the mesencephalon and rhombencephalon were essentially similar between our study and that of Blaas for samples with CRL's between 10 and 30 mm. Our observations that volume data in the present study were substantially similar to Blaas' sonoembryologic data indicate that our present data are potentially useful.

It is known that almost all measurements increase during the embryonic period; thus, linear measurements correlate both with each other and with age. In the current study, all parameters correlated with CRL (Table 1, Supplemental Figure 1). However, this basic analysis does not consider stage-specific features, which are important for precise diagnostics. When we analyzed the relationship of the parameters with CS, several measurements showed non-monotonic increases (i.e., the relationship plateaued, with a local

maximum observed c. CS19–20). Rousian et al.⁸ measured the relationship of numerous parameters with CS using 3D sonography and found that brain cavity volume increased with the quadratic function of the CS. The mean brain cavity volume in our study was comparable to that reported by Rousian et al. from CS13 to 17, but not with the quadratic function they used after CS 18 (Figure 5). Analyzing why such discrepancies arise may provide clues for further understanding stage-specific morphological features during development.

Linear measurements, which can also be used to estimate volume, may be preferable to other measurements because they are related to both brain development and growth. Thus, BT is a good marker for estimating human embryonic brain development and growth, as has been mentioned in previous studies^{1,4,7,13, 21}. The present study included embryos at earlier stages (between CS13 and CS15) in which the telencephalon was not prominent; thus, our results demonstrated that linear measurement values, such as BT and volume, are useful between CS13 and CS15.

It is difficult to compare our linear measurements with most previous

sonographic measurements^{3,5,6,7}, as the measurements used in the present study were selected from classical embryonic studies^{14,15}. Thus, with the exception of MH and ML, most of the linear measurement definitions we employed differed from those of recent studies^{5,9}. Using sonography, Tanaka et al.⁹ presented length measurements (including ML and MH) at every day of gestation between days 49 and 69. The length of ML in our study was shorter than that of the Tanaka at all stages between CS 15 and 23. The MH length in our study was also shorter than that of Tanaka et al. between CS 15 and 20, but larger after CS 21 (data not shown). Note that the comparison may not be entirely reliable as we compared the ML and MH data using the predicted CS from the day of gestation¹³. Selection and reevaluation of linear measurements that allow comparisons of data among sonoembryonic studies will be necessary for future studies. Further, the relationship between CS and embryo age is a critical issue to consider. Embryological studies demonstrate that considerable variability is observed in the size and developmental stage among human embryos at a given gestational age²². Thus, the embryonic age that is used in

clinics cannot be used to determine the developmental stage (CS), as prenatal development may not proceed at the same speed in every embryo.

The present study provided a morphometric analysis from staged human embryos using MR microscopic data. Morphometric data, according to human embryonic stages, are valuable for correcting and comparing sonographic data. The present approach may contribute to improvements in prenatal diagnostics by enabling the selection of more suitable measurements during earlier embryonic stages.

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359

Figure legends

Figure 1. MR images of midsagittal and transverse sections

(A-i) A human brain at CS23. The plane corresponding to the transverse section is indicated by a red dashed line on the midsagittal section, while the plane corresponding to the midsagittal section is indicated by a red dashed line on the transverse section. The plane was shifted from the “true” midsagittal section (indicated by a blue dashed line) because the “true” line does not include the telencephalon.

FOa: fronto-occipital diameter (primordium chiasmatis), FOb: fronto-occipital diameter (velum transversum), ML: mesencephalic length, MH: mesencephalic height, CL: cerebellar length; CH: cerebellar height, BT: bitemporal diameter (i.e., the distance between the lateral surface of the right and left temporal prominences).

(A-ii) Boundaries between the three primary brain vesicles were established by drawing a perpendicular line connecting the dorsal and ventral primary fissures,

separating the prosencephalon from the mesencephalon and the
mesencephalon from the rhombencephalon.

Pr: prosencephalon, Me: mesencephalon, Rh: rhombencephalon, Md: sum of Pr,
Me, and Rh.

Measurements were obtained from two previous studies (Desmond and
O’Rahilly, 1981; Levitan and Desmond, 2009).

(B) Human brain at CS16.

(C) Human brain at CS13.

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Figure 2. Embryonic brain length measurements according to Carnegie stages.

Figure 3. Area measurements between CS13 and CS23.

The rhombencephalon in our data is compared with “whole cerebellum” defined
in the previous study¹⁵.

Figure 4. Comparison of the present volume measurements with Blaas’ study.

(A) Increase in brain cavity and whole body volume in relation to the CRL.

(B) Prosencephalon, mesencephalon, and rhombencephalon volumes in relation to the CRL.

Blue: the present study, red: data from Blaas' study (pp 76 in Ref. 20). The prosencephalon volume was calculated as the sum of the hemispheres and the diencephalon.

Figure 5. Brain cavity volume in relation to the CS.

The present volume measurements were compared to those reported by Rousian et al.

The mean volume of our data overlapped, from CS13 to 17, with the quadratic function employed by Rousian et al⁸.

Supplementary Figure 1. Correlation between the seven length segments measured and the CRL. The data imply that brain size measurements are useful indicators of linear embryonic neural development.

Table 1. Correlation between CR-length and measured segments

Segment (Ymm)	Present study				Desmond & O'Rahilly (1980)			
	a	b	n	r	a	b	n	r
FOa	0.21	0.64	101	0.93	0.25	-0.57	83	0.92
FOb	0.28	0.36	101	0.95				
BT	0.34	-0.68	101	0.96	0.27	-0.78	75	0.97
ML	0.16	0.77	101	0.94	0.17	0.32	83	0.90
MH	0.14	-0.01	101	0.96	0.12	-0.29	85	0.92
CL	0.07	0.17	101	0.95	0.02	0.80	74	0.14
CH	0.06	-0.22	101	0.91	0.07	-0.06	77	0.52

CRL; Crown-Rump length, r; correlation coefficient

Table 2. Correlation between Carnegie stages and measured areas

Area (Y mm ²) = $a \times e^{b[CS]}$	Present study				Levitan & Desmond (2009)			
	$a \times 10^{-2}$	$b \times 10^{-1}$	n	R ²	$a \times 10^{-2}$	$b \times 10^{-1}$	n	R ²
Median section	6	3.11	101	0.92	3.33	4.37	52	0.96
Prosencephalon	0.6	3.88	101	0.96	0.74	4.94	58	0.95
Mesencephalon	0.8	3.26	101	0.95	2.92	3.84	58	0.91
Rhombencephalon *	11	2.35	101	0.85	0.03	4.95	52	0.84

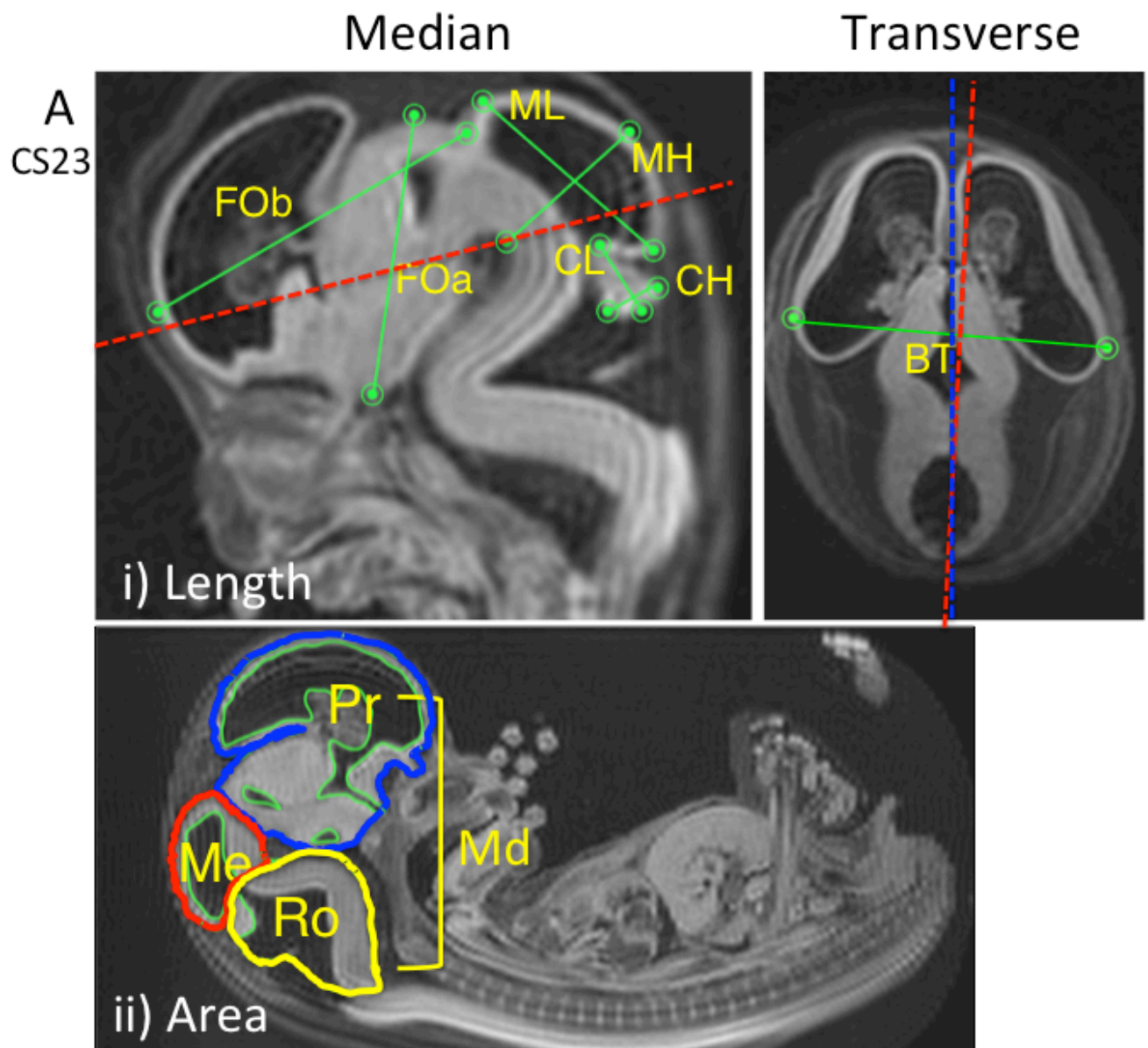
CS = Carnegie stages; *, whole cerebellum in Levitan & Desmond (2009)

Table 3. Brain volume of human embryos measured by manual segmentation

Carnegie stage n		Whole brain					Prosencephalon					Mesencephalon					Rhombencephalon				
		mean volume (mm ³)					mean volume (mm ³)					mean volume (mm ³)					mean volume (mm ³)				
		total	(SD)	tissue	cavity	ratio	total	(SD)	tissue	cavity	ratio	total	(SD)	tissue	cavity	ratio	total	(SD)	tissue	cavity	ratio
13	5	2.1	0.7	1.2 /	0.9	0.82	0.5	0.2	0.3 /	0.2	0.77	0.3	0.1	0.2 /	0.1	0.40	1.3	0.4	0.7 /	0.7	0.96
14	9	5.7	1.4	2.6 /	3.1	1.16	1.2	0.4	0.7 /	0.6	0.88	0.7	0.1	0.4 /	0.3	0.60	3.8	0.9	1.6 /	2.3	1.43
15	9	11.4	1.6	5.5 /	6.0	1.10	2.6	0.4	1.5 /	1.2	0.79	1.3	0.2	0.8 /	0.5	0.67	7.5	1.2	3.2 /	4.3	1.34
16	10	16.3	2.6	7.4 /	8.9	1.20	4.1	1.1	2.1 /	2.0	0.96	2.0	0.4	1.2 /	0.9	0.74	10.1	1.3	4.2 /	6.0	1.45
17	10	29.9	6.2	12.2 /	17.8	1.46	9.0	2.5	4.3 /	4.7	1.11	3.9	1.0	1.9 /	2.0	1.04	17.1	3.0	6.0 /	11.1	1.84
18	9	57.7	7.5	27.6 /	30.1	1.09	19.3	2.7	9.8 /	9.6	0.98	8.1	0.9	4.1 /	4.0	0.98	30.3	4.8	13.7 /	16.6	1.21
19	10	79.0	8.9	43.9 /	35.1	0.80	29.9	4.6	17.1 /	12.8	0.75	11.6	1.2	6.6 /	4.9	0.74	37.5	4.9	20.1 /	17.4	0.87
20	10	81.9	19.0	52.8 /	29.1	0.55	36.8	8.2	23.0 /	13.8	0.60	11.3	2.6	6.8 /	4.5	0.66	33.8	9.0	22.9 /	10.8	0.47
21	10	145.1	16.6	95.3 /	49.8	0.52	74.0	14.5	47.5 /	26.5	0.56	19.0	2.8	12.5 /	6.5	0.52	52.1	6.2	35.3 /	16.9	0.48
22	9	206.4	39.0	135.2 /	71.1	0.53	115.5	29.0	70.5 /	45.0	0.64	25.7	4.1	17.9 /	7.8	0.44	65.2	10.2	46.8 /	18.3	0.39
23	10	286.3	61.7	189.1 /	97.2	0.51	184.5	50.5	111.0 /	73.5	0.66	28.9	4.0	21.9 /	7.0	0.32	73.1	10.0	56.3 /	16.7	0.30

Table 4. Calculation of brain volume from length measurements

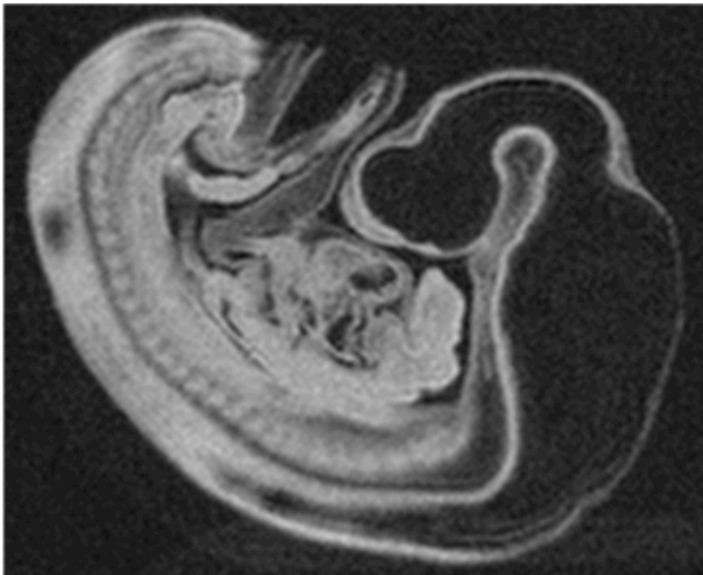
Formula				
V (mm ³) = a	[X][Y][Z]+b	a	[X][Y][Z]	+b r
Volume with ventricles				
Whole brain		0.52	[BT] ³	26.2 0.97
Prosencephalon		0.92	[FOa] ³	-9.13 0.86
		0.49	[FOb] ³	-8.21 0.93
		0.34	[BT] ³	4.05 0.98
		0.59	[FOa][FOb][BT]	-7.50 0.97
Mesencephalon		0.70	[MH] ³	3.27 0.94
		0.28	[ML] ³	0.90 0.95
Rhombencephalon		18.1	[CH] ³	19.8 0.80
		11.2	[CL] ³	9.87 0.92
Volume without ventricles				
Whole brain		0.35	[BT] ³	12.7 0.98
Prosencephalon		0.57	[FOa] ³	-6.39 0.88
		0.30	[FOb] ³	5.18 0.94
		0.21	[BT] ³	2.11 0.99
		0.36	[FOa][FOb][BT]	-5.03 0.97
Mesencephalon		0.53	[MH] ³	1.42 0.96
		0.21	[ML] ³	-0.21 0.95
Rhombencephalon		15.1	[CH] ³	10.3 0.85
		8.99	[CL] ³	2.68 0.94



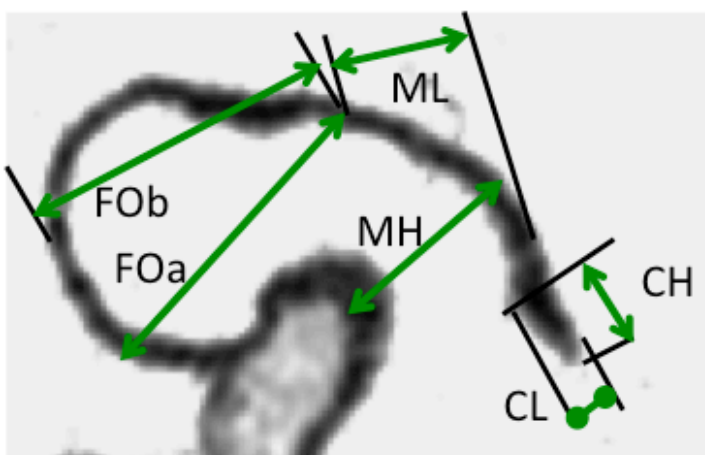
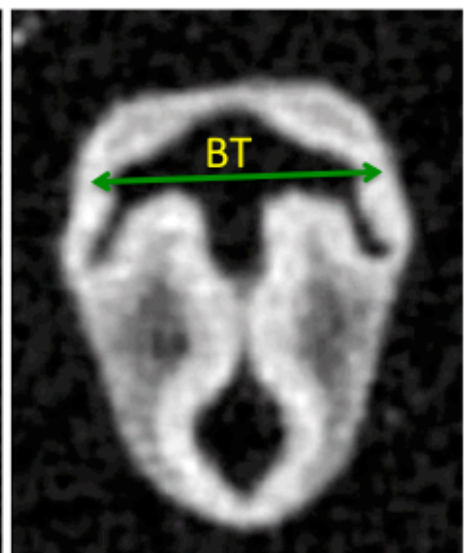
Median

Transverse

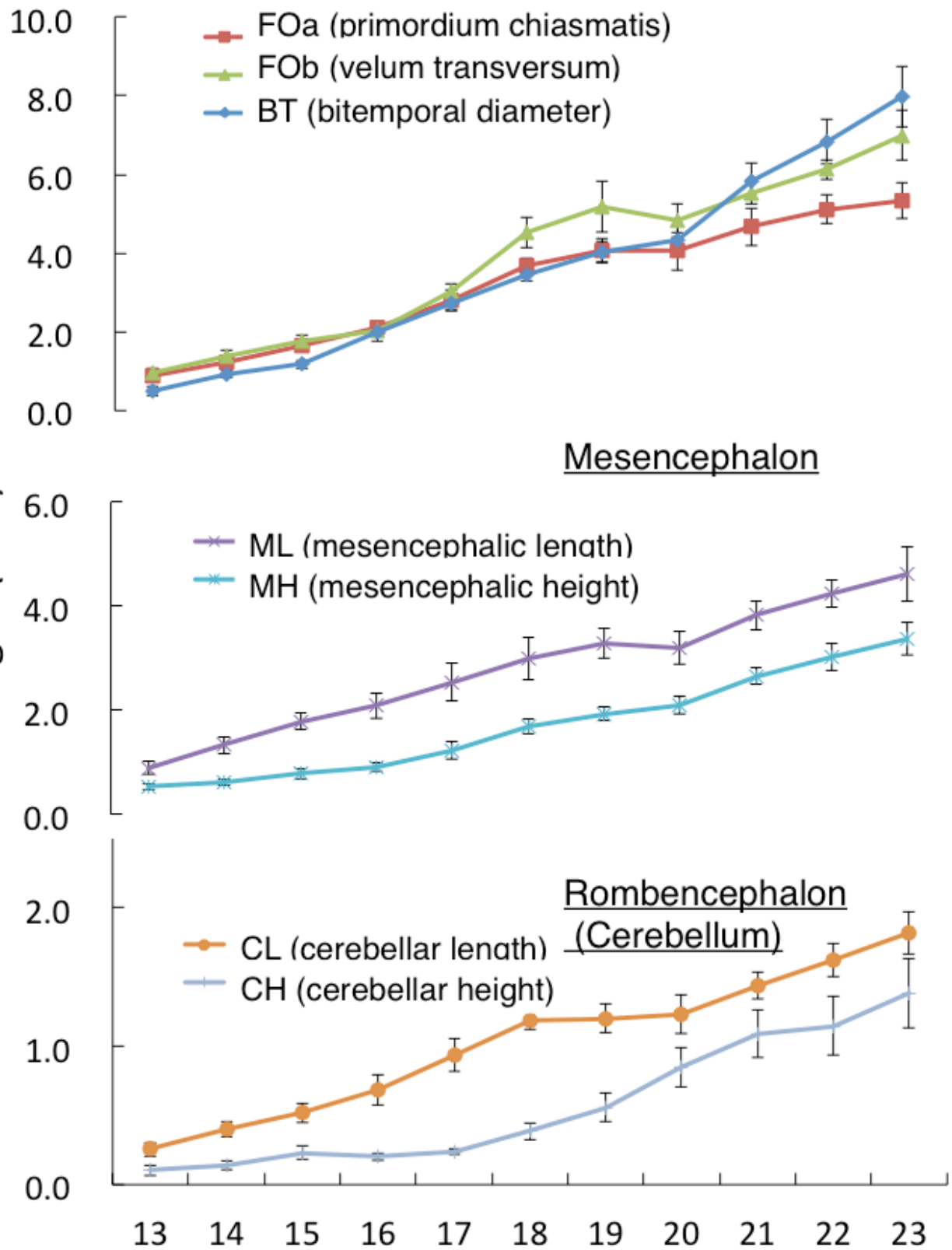
B
CS16



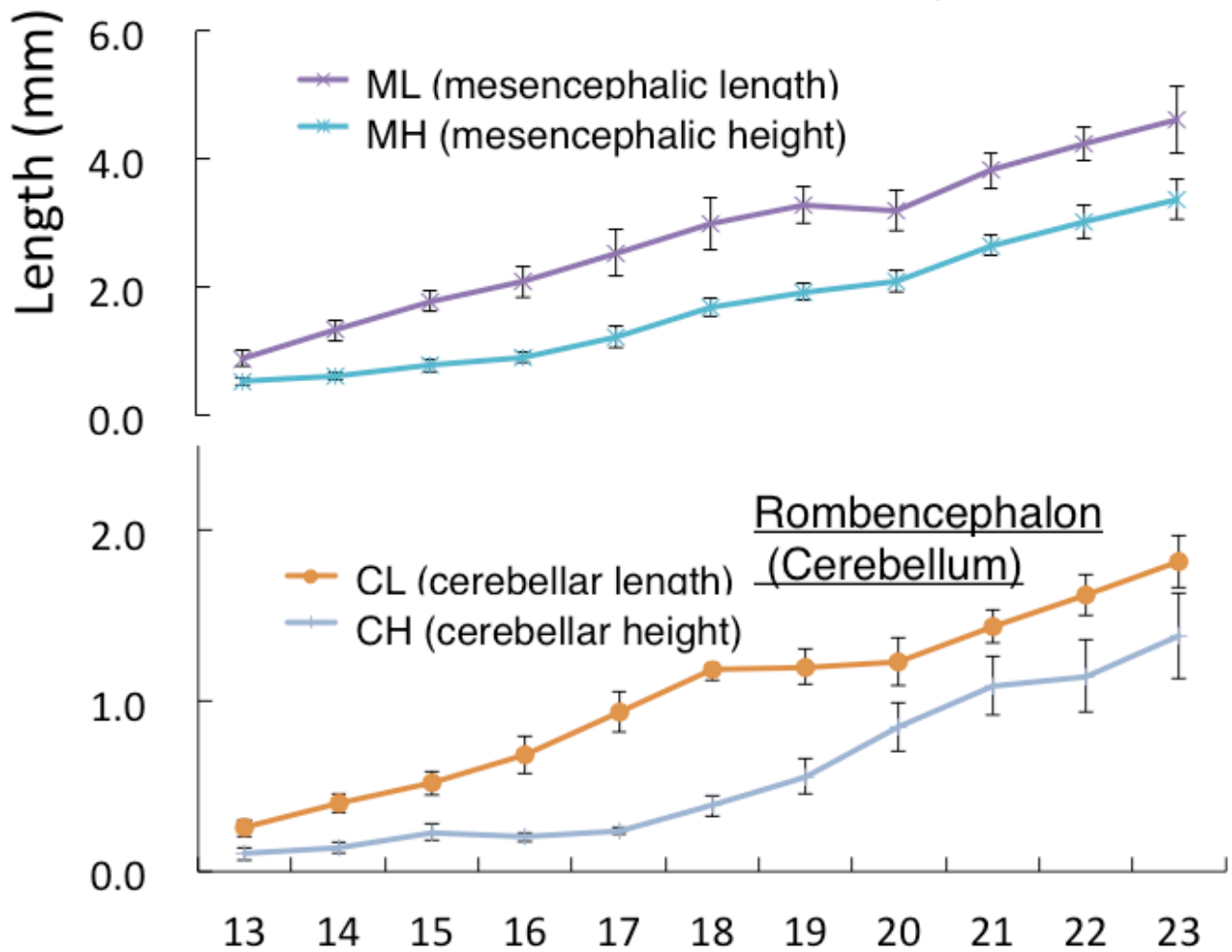
C
CS13



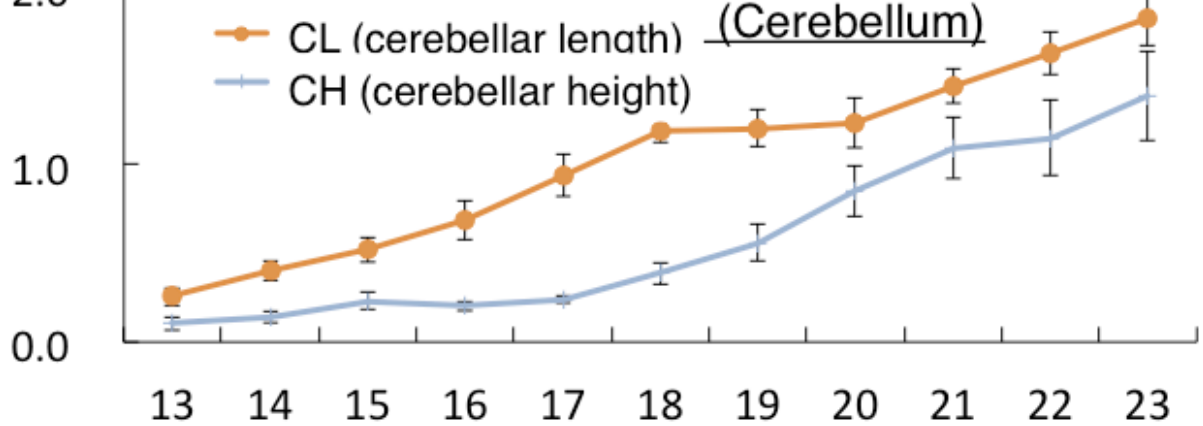
Prosencephalon



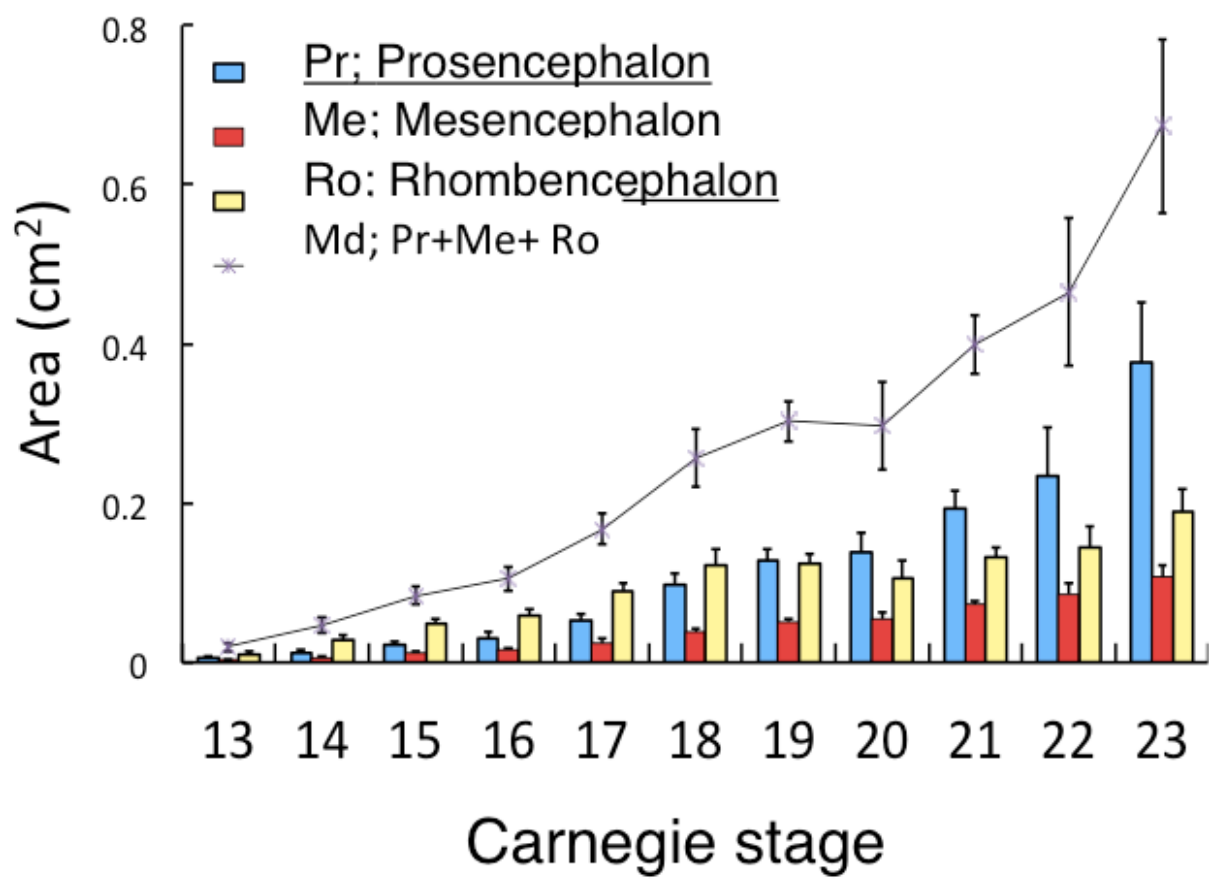
Mesencephalon



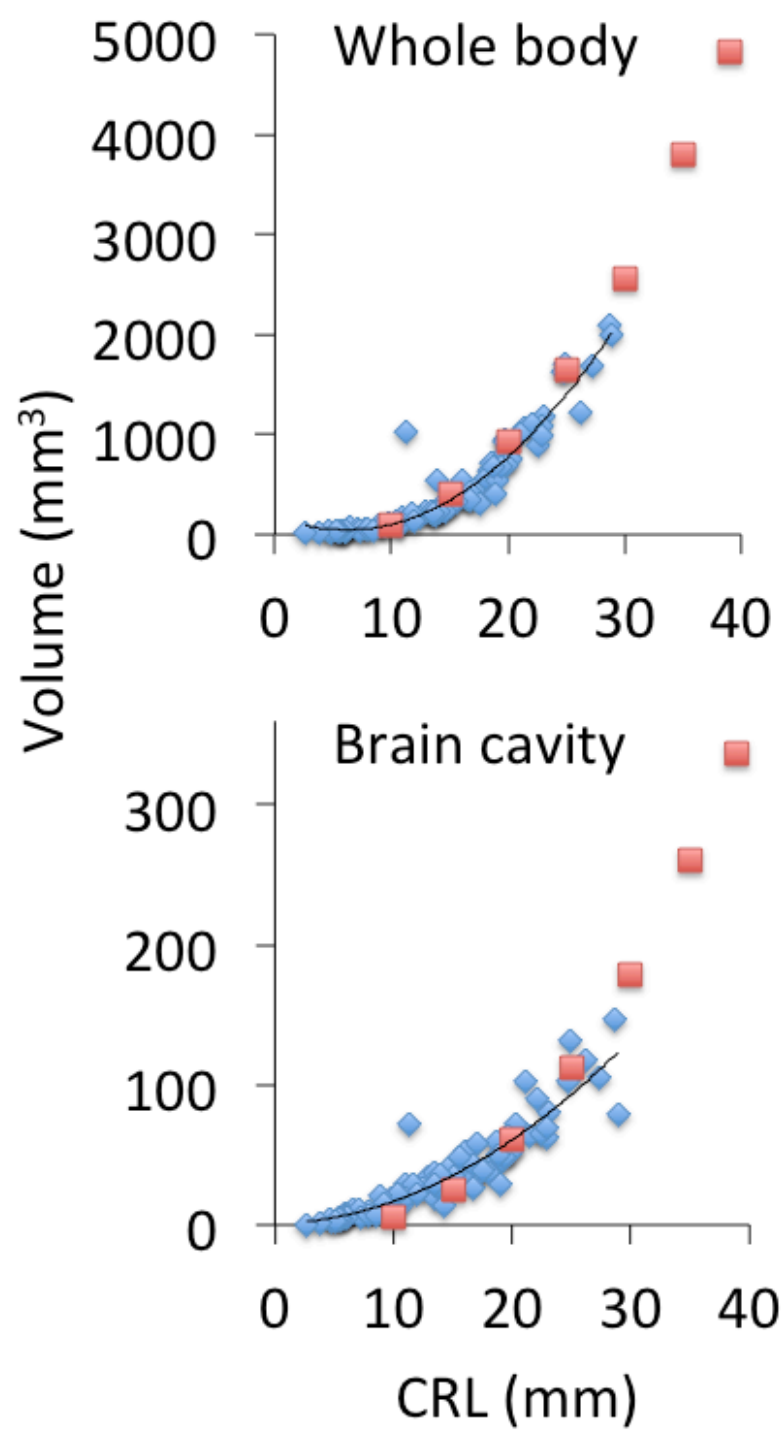
Rombencephalon (Cerebellum)



Carnegie stage



A



B

