MR volumetry of total intracranial and brain volume in normal adult population aged 40 years old and above

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***Abstract*:** This study aimed to determine the total intracranial volume, total brain volume and total intracranial volume to total brain volume ratio among the male and female subjects in normal healthy subjects aged 40 years old and above. This was a retrospective study involving 58 subjects aged from 41 to 77 years old. The study was approved by the institutional review board. Magnetic resonance imaging of the brain performed using General Electric Signa Horizon LX 1.0 Tesla scanner. Magnetic resonance images were obtained in T1 sagittal and axial sections with 5-millimetre thickness with 2-millimetre gap. The images acquired were stored in the hospital's Picture Archiving and Communications system and viewed using Osirix image viewer version 3.2.1. A single observer validated by an experienced neuroradiologist with more than 10 years' experience performed volumetric analysis. Mean (SD) of total intracranial volume was 1397.06cm^3 (132.51cm^3) for all subjects. The mean total intracranial volume for male subjects was 1496.12cm^3 (100.08cm^3). For female subjects, the mean total intracranial volume was 1310.79cm^3 (90.34cm^3). The mean total brain volume for all subjects was 1245.29cm^3 (125.34cm^3). The mean total brain volume for the male subjects was 1338.05cm^3 (91.96cm^3). For the female subjects, the mean total brain volume was 1164.49cm^3 (89.61cm^3). Mean total brain to intracranial volume ratio for all subjects were 0.8911 (0.0245). Mean total brain to intracranial volume ratio for male subjects was 0.8946 (0.0276). Mean total brain volume to total intracranial volume ratio for female subjects was 0.8881 (0.0214). This study showed no significant difference in mean total intracranial volume, mean total brain volume and total brain volume to total intracranial volume ratio between male and female. However, the study obtained valuable normative data for estimation and predicting future degenerative events in our population.

***Keywords*—Intracranial volume, brain volume, MRI, volumetry**

1 INTRODUCTION

Magnetic Resonance Imaging (MRI) has significantly accelerated many studies involving the brain with more researchers looking into not only anatomy and structural aspects of the brain, but also functional aspect due to excellent soft tissue discrimination (1). MRI also enables researchers to study the changes involving intracranial volume, brain volume and compartmental volumes, giving valuable data regarding the normal human brain morphological changes and in certain degenerative diseases or psychiatric illnesses (2)(3). In the clinical settings however, Computed Tomography (CT) is more widely used than MR imaging due to faster acquisition speed, lower cost, and its ability to answer a range of clinical questions in short examination time. However, only a limited number of automated segmentation methods currently exist for head CT images (4).

Intracranial volume measurement has long been studied by researchers because of its usefulness in recognizing changes within the human brain. Intracranial volume is defined as the total volume within the cranial space, which includes the brain, meninges and cerebrospinal fluid. Previously data gathered from autopsies considered to be the gold standard in measuring total intracranial volume. However, problems surrounding the autopsy process regarding presence of concomitant illness, long intervals between death and brain removal and weighing in different conditions may or may not affect the data gathered. MRI as a non-invasive method of study has eliminated inherent difficulties that come with autopsy process, thus making the measurement of brain and its anatomical parts much more accurate.

Intracranial volume measurement provides stable and accurate data in studying and estimating the volumetric changes within the cranium and its contents. Intracranial volume measurement can be used as a predictor to degenerative brain disease in early stages when measured together with total brain volume or ventricular volume, such as in patients with Alzheimer disease, schizophrenia, bipolar disorders or other conditions such as Huntington's disease (5). It can also be used as a predictor for severity in patients with these conditions (6–9).

The brain volume is also affected by normal aging process as well as various other neuropsychiatric illnesses such as schizophrenia and Alzheimer disease. The study of the human brain volume which dated back a century ago started with autopsy and later using computed tomography and MRI. It is estimated that the brain shows decline in volume and/or weight around 2-5% per decade after the age of 40 years old with brain volume showing marked increase in age more than 70 years old (2,10). With the present of diseases such as schizophrenia or Alzheimer disease, the brain volume can also reduce markedly (11). In these cases, brain atrophy is measured as brain volume change between two examination time points. The interval between examinations must be sufficiently large, in order to reliably detect significant atrophy (12). The inflammatory component of multiple sclerosis (MS) can be focal or diffuse and is currently associated with neurodegenerative processes that lead to irreversible tissue damage and neuronal loss in patients, that can correspond to brain atrophy (13), in which MRI provides a useful tool in volume measurement especially in brain atrophy (14). This also suggest that morphometric measurements of brain volume could be a promising non-invasive biomarker in assessing the volumetric changes in MS patients relating to disability progression during the course of the disease (15). In recent development, volumetric magnetic resonance imaging currently a promising imaging technique that can also provide valuable input in evaluation of non-lesional pharmacoresistant childhood epilepsy (16).

Total intracranial volume and total brain volume can be obtained from MRI as volumetric measurements using MRI are significantly more sensitive and definitive than visual inspection alone. With the MRI, volumetry techniques have been more optimized and more new techniques have been developed for accurate measurement and volumetry of the brain. MRI itself can be performed in various planes such as sagittal, axial and coronal using manual, semi-automated or automatic volumetric methods. Studies showed that there are no differences in total intracranial volume measured in T1-weighted or T2-weighted images (17). However, in general total intracranial volume can be measured manually from T1-weighted images. The differences between manual and automated methods of volumetry are documented in other literatures, although some show no significant differences between the two methods (18).

This study aimed to determine the total intracranial volume, total brain volume and total intracranial volume to total brain volume ratio in the normal healthy subjects aged 40 years old and above and among the male and female subjects. Data obtained can later be used later in predicting the aging process or degenerative changes in patients with Alzheimer disease and patients with psychiatric illnesses such as schizophrenia and bipolar disorder.

2 MATERIALS AND METHODS

This was a retrospective study involving subjects who underwent MRI under previous research grant. The age of the subjects ranged from 41 to 77 years old with 58 subjects recruited. The study was approved by the institutional review board. Subjects with focal neurological deficit, history of psychiatric illness or dementia, history of epilepsy, substance abuse, head trauma and abnormal MRI brain findings were excluded from the study.

MRI was performed using Signa Horizon LX 1.0 Tesla scanner by General Electric. MRI images were obtained in T1 sagittal and axial sections with 5-millimetre thickness with 2-millimetre gap. The images acquired were stored in the hospital's PACS system and viewed using Osirix image viewer version 3.2.1. Images were analysed using an Apple MacPro workstation with 2.66GHz Dual Core Intel Xeon processor. Monitor for the workstation was Apple Cinema High Definition Display 23-inch panel with 1920 x 1200 pixel resolution. Volumetric analysis was performed by a single observer validated by an experienced neuroradiologist with more than 10 years' experience.

Tracing of intracranial cavity and brain was made three times for each slice to get an average measurement. A difference of 5.0 cm^2 between the measurements was allowed. The average measurement for each slice was summed together to get the total area in centimetre square. Intracranial volume and brain volume would be calculated using alternate slice volumetric measurement by multiplying the total area of the intracranial or brain, in the unit of square centimetres (cm^2) with the slab thickness (1.4cm). By using this method, the total intracranial volume and total brain volume was then obtained in cubic centimetres (cm^3).

The inner boundary of intracranial cavity outlined was dura mater below the inner table and generally visible as a white line. Where the dura mater was not visible, the cerebral contour was outlined. Other landmarks were the under surfaces of the frontal lobe, the dorsum sellae and clivus. The inferior limit of segmentation was set as a line draw between the craniovertebral junctions at the attachment of dura to the posterior cutting across to the anterior arch of the atlas (C1) (Figure 1).

For the delineation of the boundaries of the intracranial during measurement especially for the parts that the dura lining was not clearly stated on the images despite adjusting the optimal contrast and increasing the size of the images, we used the axial view on T1WI and/or T2WI for our references.

For total brain volume measurement, manual tracing performed by delineating the brain surface from the dura and the inner table. In parts where there was no clear demarcation between the structures, the most visible part of the brain surface was measured (Figure 2).

The mean (SD) of total intracranial volume and total brain volume were calculated and analysed using IBM SPSS version 20. Assumption of normal curve was met, and data was analysed using independent t-test. p-value of less than 0.05 is taken as significant.

Figure 1: Sagittal T1 image showing the manual delineation of the intracranial cavity. The inferior limit of segmentation was set as a line draw between the craniovertebral junctions at the attachment of dura to the posterior cutting across to the anterior arch of the atlas (C1).

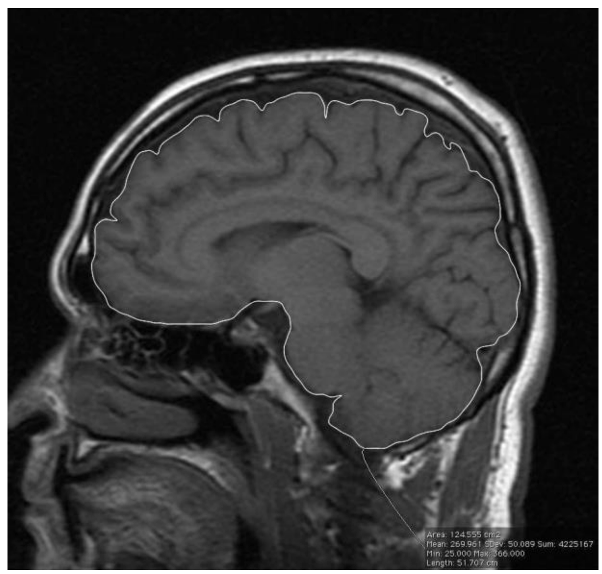
Figure 2: Sagittal T1 image showing the manual delineation of the brain. Manual tracing performed by delineating the brain surface from the dura and the inner table. In parts where there was no clear demarcation between the structures, the most visible part of the brain surface was measured.

3 RESULTS

A total of 58 Malay adults aged 40 years old and above were included in this study. The mean (SD) age was 56.62 (8.16) years old, ranging from 41 to 77 years old. The sample was almost equally distributed between the sex group; 53.4% were female (n=31) and 46.6% were male (n=27).

Mean (SD) of total intracranial volume was 1397.06cm^3 (132.51cm^3) for all subjects. The mean total intracranial volume for male subjects was 1496.12cm^3 (100.08cm^3). For female subjects, the mean total intracranial volume was 1310.79cm^3 (90.34cm^3) (Table I).

Table I: Mean intracranial volume (cm3) for all subjects (n=58)

Sex	n	Mean (cm^3)	SD (cm^3)	Minimum, maximum (cm^3)	95% CI
Male	27	1496.12	100.08	1281.08,1797.36	1456.53, 1535.71
Female	31	1310.79	90.34	1153.28,1518.90	1277.65, 1343.93
Total	58	1397.06	132.51	1153.28,1797.36	1362.22, 1431.91

The mean total brain volume for all subjects was 1245.29cm^3 (125.34cm^3). The mean total brain volume for the male subjects was 1338.05cm^3 (91.96cm^3). For the female subjects, the mean total brain volume was 1164.49cm^3 (89.61cm^3) (Table III).

Table III:. Mean brain volume (cm3) for all subjects (n=58).

Sex	n	Mean (cm^3)	SD (cm^3)	Minimum, maximum (cm^3)	95% CI
Male	27	1338.05	91.96	1132.42,1594.99	1301.67 ,1374.43
Female	31	1164.49	89.61	986.38,1344.49	1131.62 ,1197.36
Total	58	1245.29	125.34	986.38,1594.99	1212.33 ,1278.24

Mean total brain to intracranial volume ratio for all subjects were 0.8911 (0.0245). Mean total brain to intracranial volume ratio for male subjects was 0.8946 (0.0276). Mean total brain volume to total intracranial volume ratio for female subjects was 0.8881 (0.0214) (Table V).

Table V: Brain volume to intracranial volume ratio for all subjects (n=58).

Sex	n	Mean	SD	Minimum, maximum	95% CI
Male	27	0.8946	0.0276	0.8260, 0.9407	0.8837, 0.9056
Female	31	0.8881	0.0214	0.8430, 0.9301	0.8802, 0.8960
Total	58	0.8911	0.0245	0.8260, 0.9407	0.8847, 0.8976

There was no statistically significant difference of mean total intracranial volume, mean total brain volume and total intracranial volume to total brain volume ratio between male and female subjects (Tables II, IV and VI).

Table II: Comparison of mean intracranial volume (cm^3) to sex. Independent t-test applied.

Variable	Mean (SD) (cm^3)		Std. Error Mean		Mean difference (95% CI)	*t* statistic (df)	*p*-value*
	Male	Female	Male	Female			
Sex	1496.12 (100.08)	1310.79 (90.34)	19.26	16.23	185.32 (135.23,235.42)	7.411 (56)	0.932

Table IV: Comparison of mean brain volume (cm^3) according according to sex. Independent t-test applied.

Variable	Mean (SD) (cm^3)		Std. Error Mean		Mean difference (95% CI)	*t* statistic (df)	*p*-value*
	Male	Female	Male	Female			
Sex	1338.05 (91.96)	1164.49 (89.61)	17.70	16.09	173.55 (125.72,221.39)	7.268 (56)	0.708

Table VI: Comparison of brain volume to intracranial volume ratio according to sex. Independent t-test applied.

Variable	Mean (SD)		Std. Error Mean		Mean difference (95% CI)	*t* statistic (df)	*p* value*
	Male	Female	Male	Female			
Sex	0.8946 (0.0276)	0.8881 (0.0214)	0.0053	0.0038	0.0065 (-0.0064,0.0194)	1.012 (56)	0.145

4 DISCUSSIONS

A total of 58 subjects were recruited from a total sample size of 81. This corresponded to 71% response rate from the total sample size. This was due to limited number of subjects aged 40 years old and above within the research database from our PACS system. From 58 subjects recruited, there were almost equal numbers of subjects according to sex with 27 were male and 31 were female who fulfilled the inclusion and exclusion criteria. The number of subjects recruited was comparable to a few studies published.

Matsumae *et al.* studied age related changes in intracranial compartment volumes in normal adult subjects using MRI (19). They recruited a total of 49 subjects with age ranging from 24 years old to 80 years old to determine age related changes in intracranial, brain, ventricular and extra ventricular cerebrospinal fluid volumes. A much larger sample size was recruited by Kruggel *et al.*, who recruited a total of 502 healthy adult subjects for volumetry study of head compartments using MRI (6). A total of 254 male subjects and 248 female subjects with age ranging from 16 years old to 70 years old participated in the study. Blatter *et al.* also recruited larger number of subjects to our study. Their study involved 194 healthy adult subjects from 16 years old to 65 years old to study volumetric parameters of the brain (20).

In comparison to other studies in our literature reviews, a much larger cohort would have enabled us to obtain much accurate volumetric measurements of the intracranial cavity, the brain and its compartments. The mean total intracranial volume derived from our study showed that the cranial capacity among our Asian study population did not differ greatly from other population such as Europeans. In addition, our results were also almost similar with some anthropologic studies such as Beals *et al.* (21). The total intracranial volume among Asian population from their study was 1380.00cm^3 (83.00cm^3) which was close to our results.

Among male and female subjects, published studies such as by Narr *et al.* and Arango *et al.* also showed results that were not dissimilar to our results (22,23). This could mean that even in Asian population, the total intracranial volume among male and female subjects was comparable to other population and races, although the population in our study has an average age higher than other studies.

From the mean total brain volume obtained for all subjects in this study, we noted that the mean total brain volume was close to the results obtained in study by Matsumae *et al.* (19). In their study involving 49 healthy adult volunteers, the mean total brain volume for all participants was 1227.00cm^3 (135.00cm^3). The difference of the results obtained in their study with our study was approximately 1.5%, signifying close resemblance of the findings obtained in both studies. In our study, the mean age of our subjects was 56.62 (8.16) while the mean age of the subjects in their study was 56.00 (16.00). Therefore, the age difference in both studies was not greatly differs from one another. Comparison with the study by their research group also implied that with the near similar findings of the mean total brain volume obtained, we could indicate that the difference of population between Malay and American population were not large. This could also mean that the mean total brain volume obtained in either population might be representative in both populations.

Our result also was almost similar to the results obtained by Blatter *et al.* (20). They conducted a study involving 194 healthy subjects within the American population with age range of 16 years old to 65 years old. The mean total brain volume obtained from their study was 1273.26cm^3 (155.62cm^3). Their result showed a 2.2% difference of mean total brain volume from our result. With a larger sample size of 194, the result obtained in their study was more significant. Their findings also signified that the mean total brain volume among normal healthy adults in both Asian and American population does not differ significantly from one another, thus implied that the result in either population could be replicated in each study population. The difference in the techniques utilized was also noted, with our study using the manual volumetry technique while Blatter *et al.* used a semi-automated technique using a third-party commercial software (24). The results for both male and female subjects in this study corresponded to previous published results by Matsumae *et al.* In their study, the mean total brain volume for male subjects was 1302.00cm^3 (112.00cm^3) and 1143.00cm^3 (105.00cm^3) for female subjects. The results were not differing significantly with our study not only in regard to the mean brain volume for both male and female but also for mean intracranial volume.

In comparison with the study by Reite *et al.*, our study also showed almost similar results with the previously published data (7). Their study which was conducted in a slightly larger sample size of 89 with almost equal distribution in between both sexes showed a mean total brain volume of 1354.00cm^3 (111.00cm^3) for male subjects and 1216.00cm^3 (106.00cm^3) for female subjects.

The total brain volume and total intracranial volume ratio was calculated for all subjects in this study and further divided according to the sex group. Both ratios for male and female subjects showed no statistically significant difference among them. The results could suggest that intracranial volume and brain volume in normal and healthy adult Malay population have no significant difference in respect to sex difference. Both sexes show similar cranial capacity and volume ratios. The results also showed that in Western population, the ratio of mean total brain volume to total intracranial volume was almost similar to our population. Comparing to another published data by Kruggel *et al.*, our results closely resemble the data obtained from his study. Their study results showed the ratio of mean total brain volume to total intracranial volume among all subjects was 0.8750 (0.0175). The ratio for male subjects was 0.8730 (0.0170) while the ratio for female subjects was 0.8770 (0.0180). There was no statistically significant difference between the ratios in those two sex groups in their study. Furthermore, the results were almost as the same as our study, further adding to the similarities in intracranial and brain volumes between the Malay population and Western population. This was then further emphasized by the large number of sample size recruited in their study (n=502).

As for the method of measurement, either by measuring the total brain volume or intracranial volume, some suggests these measurement methods have their own advantages and disadvantages, as compared to other methods. Normalisation to age and sex of the measurements are being proposed in more studies to avoid bias. Given that brain volumes are increasingly used as clinical indicators, a robust and unbiased reference to the normal ranges of the brain structures volumes is necessary to reduce the false decisions caused by misalignment due to the patients' sex or age (25). Another factor is inter-individual variation in brain volume, which can be normalised to the size of the intracranial cavity (26).

This study has few limitations. Although Malay race represent the majority in the country, inclusion of other races such as Chinese and Indians would make the results more representative to Asian population at large and our country specifically. Moreover, other confounding factors such as height and body weight were not taken into consideration in this study due to limitation in data collection. Manual volumetry technique used in this study was subject to observers' skills and training, making it operator dependant and time consuming compared to semi- and fully automated volumetry. Furthermore, automated techniques are less expensive and time-consuming than manual or semiautomatic segmentation of brain structures, and more precise than qualitative visual assessment, and provide good to excellent correlation (27)(28).

5 CONCLUSION

We have measured and calculated the mean total intracranial volume, mean total brain volume and total brain volume to total intracranial volume ratio in a normal healthy adult Malay population. There was no significant difference in mean total intracranial volume, mean total brain volume and total brain volume to total intracranial volume ratio between male and female. We have obtained a valuable normative data for estimation and predicting future degenerative events in our population. Volumetry using MRI is a non-invasive and reproducible technique and relatively easy to perform with no ionizing radiation effect to the subjects. The results gathered would be most beneficial for those patients who are experiencing mild cognitive impairment or newly diagnosed neuropsychiatric disorders such as Alzheimer disease or schizophrenia.

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