Volume Estimation from Brain Magnetic Resonance Images using Gradient Filters

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Abstract

Brain volume estimation is a challenging area for research in medical domain. A quantitative analysis of the brain volume is very important for the diagnosis and tracking progression of various degenerative brain diseases in several clinical applications. This study aims to develop an automated method for estimating volume of the brain using MRI (Magnetic Resonance Imaging) data. In this paper, a novel approach of brain volume estimation using gradient based filters and volume refinement is proposed. The experiment is conducted on MRI volumetric data of total 20 patients. Live data of 10 patients is collected from Hospital and data of 10 patients is taken from publicly available Open Access Series of Imaging Studies (OASIS) dataset. The average accuracy of Brain volume estimation obtained through proposed approach with Gradient Magnitude Image Filter using OASIS data is 94.16% and using live data is 93.65%.Design of such approaches can assist radiologists by estimating brain volume and can help in determining existence and progression of neurodegenerative diseases.

Key Words: Brain volume, Brain MRI analysis, Volume estimation
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1. Introduction

MRI is a radiofrequency based technique that analyses the spinning of hydrogen atoms in the brain without making any invasion. It can be used to diagnose and measure various brain disorders. Various brain imaging techniques such as MRI, Computed Tomography (CT), and perfusion can be utilized to diagnose and measure the changes in the brain. Being non-invasive, MRI provides quantitative and qualitative data on in vivo tissues. According to the Alzheimer Research Forum, this technology can identify people who may be benefitted from treatment to delay the development of Alzheimer's.

An automatic method supported by fuzzy granulation is proposed by SyojiKobashi[1]. This method can generate a robust threshold and it can also smoothen the noise peaks in the histogram. A method that uses fuzzy information granulation and inferences was proposed by Yutaka Hata[2].It provides a detailed understanding of the human brain. Tao Song has proposed a method for partial volume segmentation in magnetic resonance images[3]. His method uses a modified probabilistic neural network. In proposed method, Smitha et al. estimated the brain tissue size using MRI [4].Stefan Bauer et al. have presented a volumetric approach for stroke patients for the selection of treatment using MRI data[5]. This method was evaluated on a small image dataset. Hassan Kastavaneh has proposed Brain extraction using isodata clustering[6].It was able to remove outliers using histogram analysis. The method was validated using the Region of Interest method. For calculation of brain volume, Bigler and Tate used a tissue segmentation based procedure (analyze).They concluded that total brain volume of subjects with mixed dementia/ neuropsychiatric disorders was 22% lower than total intracranial volume[7]. JussiTohkaet al. proposed trimmed minimum covariance determinant (TMCD), a robust and fast method of parameter estimation. The results were similar to those obtained using the expectation–maximization-like (EM-like) procedure, though they require less time to complete. The concept of the TMCD method has been proposed to allow for the robust and accurate estimation of partial volume model parameters[8].Thus research is going on but the demand for automated brain volume calculation is still quite high. This paper includes a brief review of related literature, proposed approach, results and future scope.

2. Background

2.1. Magnetic Resonance Image Representation

MR images consist of pixels. A pixel is the smallest sample of 2 dimensional element in an image. It has dimensions that are given along two axes in millimeters, which dictates in-plane spatial resolution. A voxel is the volume element, which is defined in 3 dimensional space. The slice thickness and pixel spacing contribute to calculation of voxel volume. DICOM (Digital Imaging and Communications in Medicine) is the most commonly used format for storage of MR images. These files have details of MR scan and patients. Usually a brain scan captures image sequence in the range of 250-300 images.

2.2. Analysis of MR images

The two approaches that can be used to analyze Magnetic Resonance images are ROI (region of interest) based and voxel-based. In ROI based category, volumetric analysis and visual rating method are used commonly. Volumetric methods are widely used for assessing the volume of specific temporal lobe structures while visual rating methods allow the assessment of regional atrophy and other alterations in the brain.

Currently, the gold standard method for volumetric analysis is manual outlining of region of interests. However, this method is time consuming and may have high inter-rater variability[9]. For automatic delineation of ROIs, though many methods are developed, still improvement can be achieved. Automated approaches for better delineation and more precise measurement of volume can be devised.

2.3. Voxel-based morphometry (VBM)

VBM is a voxel-based approach used to identify changes in tissue density across the entire brain using statistical methods. It avoids the need for multiple tests and allows the identification of subjects with mild cognitive impairment[10].

2.4. Methods based on Visual-Rating

The goal of this kind of methods is to provide a reliable yet accurate evaluation based on human visual rating. It was proposed that these methods could be used to identify individuals with early Alzheimer's Disease (AD) and predict which of them would become AD.

2.5. Manual outlining

Inspite of being lengthy, time consuming and rater dependent, manual estimating of region of interests is the gold standard method till today[11].

2.6. Volume estimation and analysis

Volumetric analysis of brain structures has become increasingly useful for monitoring disease progression and identifying changes in the brain's size. There has been a steady decrease in the volume of the hemisphere over the years, which can be attributed to the aging process. Regional segmentation on MRI scans is also necessary in order to obtain the accurate volumetric measurements needed for various structures. Due to the imprecise nature of the scans, the region boundaries are typically not defined. Compared to the whole brain approach, extracting the Region of Interest from MRI data requires special skills and expertise. Since there are no two brains that have the same size and shape, extracting the region automatically requires a certain level of sophistication. Techniques related to quantitative brain segmentation have been proposed to improve the method of assessing the volume changes in various medial temporal lobe structures. These methods can provide comparisons of the changes in regional volumes across different pathological states.

Many researchers have published the impact of brain volume change on cognitive levels. Henrike Wolf et-al. found that the severity of cognitive impairment was moderately correlated with the intracranial volume in case of MCI (mild cognitive impairment) patients [12]. Karen J. et al. tried to estimate intracranial volume using a single intracranial cross-sectional area using a method that relied on the slice's mid-sagittal region. They found that the cross-sectional area and inoculation volume were highly correlated[13]. Eritaia et al. have concluded in their research that the lack of methods that can accurately identify the non-pathological differences in brain volume has been a common issue in previous studies. These differences are caused by various factors such as age, sex, and body size[14]. I. Driscoll et al. have found association between differential volume loss in specific brain regions and Mild cognitive impairment. Early identification of volume loss can help detect disease onset[15].

Few researchers have used publicly available software packages for brain volume estimation and analysis. SamanSargolzaei et al. have examined the performance of three well-known softwares statistical Parametric Mapping (SPM), Free Surfer (FS) and FMRIB Software Library(FSL) in automatic estimation of brain volume. The study uses a priori knowledge of the patient population to determine which algorithm is most suitable for estimating intracranial volume. The data was then analyzed using a pediatric template. Lesser systematic bias was observed using SPM12 across the Adult Control group[16].Klasson et al. found that effective total intracranial volume from FS is biased by total brain volume[17].According to Ridgway et al. total intracranial volume is commonly used to measure inter-subject variability in the pre-morbid phase of brain volume. It can be estimated using manual or automated methods. The recent improvements in the SPM allowed us to get an unbiased and accurate estimate[18]. Richard N. et al. compared the biases using software packages. FS showed bias based on skull size while SPM showed bias related to gender and atrophy. The data revealed that the use of Intracranial volume

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estimation method can affect studies related to brain volume[19].

Currently, the methods used for estimating the volume of the brain are not very accurate due to their lack of anatomical specificity, erroneous tissue classification and substantial need of computation time.

3. Materials and Methods

3.1. Gradient filters

Image gradients are mainly used for the detection of edges in an image. They help in determining the volume of the brain by estimating the regions within the image. In MRI images, gradient magnitudes are used to identify the regions with the most contrast. Due to the existence of outliers in an image, image smoothing with edges preservation is a challenging task. Xue et al. found that the image gradient magnitude can still provide highly accurate quality prediction without using additional information[20].Usually, anisotropic diffusion techniques are used to reduce noise and preserve specific image features, such as edges.According to Beitoneet. al. ,the gradient anisotropic diffusion filter performs better in computing global reconstruction error. It performs much better in computing relative error [21]. Gradient Magnitude Recursive Gaussian computes the magnitude of the gradient of an image by convolution with the first derivative of a Gaussian[22]. In many approaches , gradient based filters are used for noise removal. Xiaobo Zhang et al. presented a new method that combines the signal detection gradient and the signal local directional variance. They found that the two basis functions can reduce the negative effects of local windows[23].

3.2. Skull stripping

“Skull stripping” refers to extraction of whole brain and separation of non-brain voxels in brain-imaging sequences. It is a key step in analysis of brain-images. The Swiss skull stripper is a module that registers an image to the patient data. The first step is of erosion of brain mask. After that level-set methods are used for accurate brain extraction.

3.3. Brain volume refinement

The goal of Brain Volume Refinement (BVeR) is to get rid of the patterns that are not consistent with the brain borders. It achieves this through an algorithm that uses an iterative evaluation process to determine the discontinuity of the image's pixel signal level. As the volume change in consecutive iterations becomes stable, the algorithm stops making corrections in brain boundary[24].

3.4. Source of Data

This research is conducted on MRI volumetric data of total 20 patients. Few of them are demented and few are non-demented patients. Data of first 10 patients is obtained from first scan of initial 10 patients of publicly available OASIS Longitudinal dataset[25]. Data of next 10 patients is obtained from Nanavati Max Superspeciality Hospital, Mumbai. The hospital has provided anonymous data i.e. Name, address, financial and educational details are not provided by the hospital. Incomplete data (data with missing values) is not considered for experimentation. In most of the research papers studied, the study size was small. We wanted to consider samples from both the datasets i.e. publicly available dataset and live dataset from hospital. Hence we considered data of 10 patients from each of the sources.

3.5. Proposed Approach

The experimentation was conducted using 3D Slicer tool[26].It is an efficient platform for faster computations on multi- dimensional images. In proposed approach , MRI volumetric data is taken as input. This data is available in nifti file format and takes approximately 33Kb memory space per patient.

Input Output

Fig. 1 Proposed model using Gradient based Filters.

Fig. 1 shows proposed approach. For noise removal, three gradient based filters- Gradient Magnitude Image (GMI) filter ,Gradient Magnitude Recursive Gaussian (GMRG) filter and Gradient Anisotropic Diffusion (GAD) filter were applied. After filtering, swiss skull stripping is applied for removal of skull (non-brain pixels). For enhancement of skull stripped volume, Brain Volume Refinement(BVeR) module is used. Finally , the brain volume is estimated by considering image dimensions and the gap between two consecutive image slices.

4. Results

To represent three dimensional volumetric data , views from all three directions are considered here. Transverse, coronal and sagittal views from volumetric MRI data of a patient are shown below at different stages.

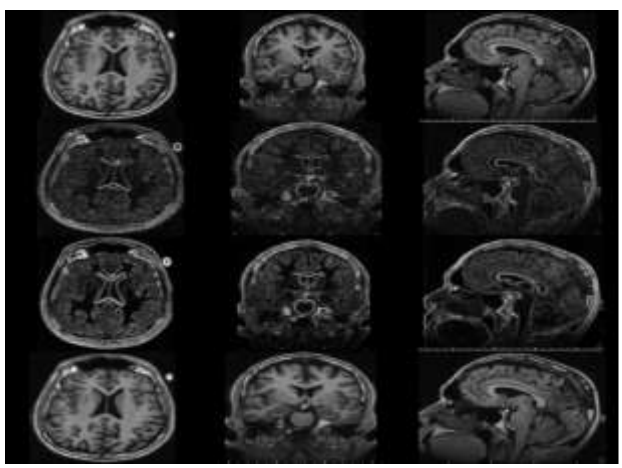

Fig. 2 Row 1- Input raw MRI images of patient 6; Row2,3,4-MRI images after GMI,GMRG and GAD filtering respectively.

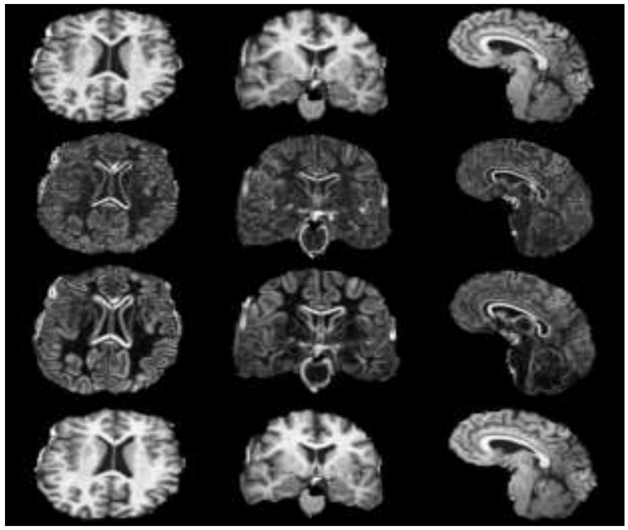

Fig. 3 Row 1- skull stripped raw MRI images of patient 6; Row2, 3, 4- MRI images after skull stripping of GMI,GMRG and GAD filtered images respectively.

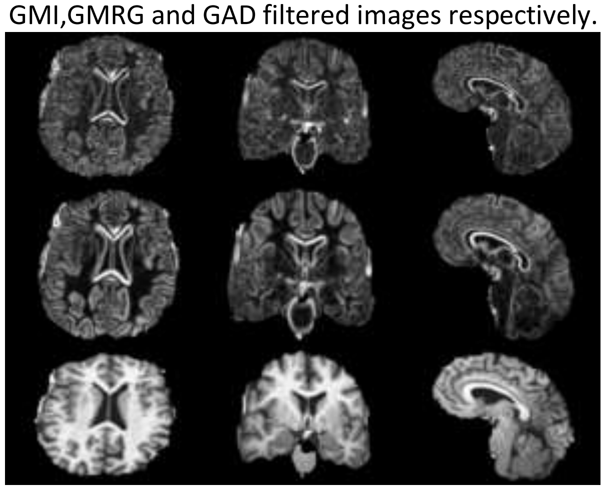

Fig. 4 Row1,2,3- MRI images after volume refinement of skull stripped GMI, GMRG and GAD filtered images respectively for patient 6.

Fig. 2 shows transverse, coronal and sagittal views of raw MRI images taken as input and transverse, coronal and sagittal views after applying GMI, GMRG and GAD filtering respectively. Fig. 3 shows all three views of skull stripped raw MRI images of same patient and MRI images after skull stripping of GMI, GMRG and GAD filtered images respectively. Similarly, Fig. 4 shows all three views of after Volume refinement of skull stripped GMI, GMRG and GAD filtered images respectively.

Table 1. Brain volumes with respective estimation accuracies for first 10 Patients.

Patient no.	**Reference Volume (CM3)**	**Volume 1 (CM3)**	**Accuracy 1 (%)**	**Filter**	**Volume 2 (CM3)**	**Accuracy 2 (%)**
Patient1	1678	1137.73	67.79	GMIF	1409.34	83.97476
				GMRG	1329.21	79.20026

				GAD	1127.58	67.18624
Patient2	1689	1365.59	80.85	GMIF	1542.96	91.35346
				GMRG	1452.42	85.9929
				GAD	1346.57	79.72587
Patient3	1272	1018.69	80.12	GMIF	1167.29	91.80345
				GMRG	1117.49	87.88684
				GAD	1011.84	79.57782
Patient4	1457	1322.54	90.8	GMIF	1455.42	99.91899
				GMRG	1424.94	97.82645
				GAD	1315.93	90.34258
Patient5	1447	1146.9	79.27917	GMIF	1323.63	91.49558
				GMRG	1276.21	88.21769
				GAD	1143.15	79.01995
Patient6	1333	1162.16	87.1596	GMIF	1332.52	99.93625
				GMRG	1315.7	98.67479
				GAD	1150.88	86.31363
Patient7	1230	1100.63	89.50249	GMIF	1228.43	99.8951
				GMRG	1194.71	97.15301
				GAD	1121.88	91.23052
Patient8	1602	1355.06	84.59133	GMIF	1565.93	97.75515
				GMRG	1458.5	91.0487
				GAD	1334.12	83.28412
Patient9	1651	1435.66	86.97807	GMIF	1563.19	94.70435
				GMRG	1496.31	90.65249
				GAD	1423.12	86.21834
Patient10	1783	1385.14	77.70292	GMIF	1617.25	90.72371
				GMRG	1578.42	88.54545
				GAD	1390.09	77.9806

Patient no.	**Reference Volume (MM3)**	**Volume 1 (MM3)**	**Accuracy 1**	**Filter**	**Volume 2(MM3)**	**Accuracy 2**
Patient11	1221.53	1118.66	91.5786	GMIF	1302.2	93.396
				GMRG	1268.21	96.1786
				GAD	1075.99	88.0854
Patient12	1445.9	1112.88	76.968	GMIF	1217.77	84.2223
				GMRG	1242.52	85.934
				GAD	1085.01	75.0405
Patient13	1375.49	1150.47	83.6407	GMIF	1240.1	90.157
				GMRG	1244.27	90.4601
				GAD	1109.45	80.6585
Patient14	1413.53	1244.94	88.0731	GMIF	1423.75	99.277
				GMRG	1416.92	99.7602
				GAD	1216.12	86.0343
Patient15	1402.98	1101.21	78.4908	GMIF	1407.11	99.7056
				GMRG	1331.02	94.8709

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				GAD	1079.66	76.9548
Patient16	1438.16	1258.19	87.4861	GMIF	1562.98	91.3209
				GMRG	1574.8	90.499
				GAD	1242.71	86.4097
Patient17	1415.5	1035.39	73.1466	GMIF	1271.14	89.8015
				GMRG	1266.16	89.4497
				GAD	1010.04	71.3557
Patient18	1366.53	1181.64	86.4701	GMIF	1337.93	97.9071
				GMRG	1312.28	96.0301
				GAD	1139.29	83.371
Patient19	1616.04	1398.98	86.5684	GMIF	1728.29	93.054
				GMRG	1688.84	95.4952
				GAD	1413.66	87.4768
Patient20	1366.73	1092.58	79.9412	GMIF	1340.68	98.094
				GMRG	1303.29	95.3583
				GAD	1060.46	77.591

Table 1 shows detailed results for 10 patients using OASIS dataset. Reference volume is taken from OASIS dataset. Volume 1 is the volume value estimated without using any filtering and volume refinement. Accuracy 1 is the estimation accuracy for volume 1. Filter column shows the name of filter applied. Volume 2 is the estimated brain volume after applying filter and volume refinement. Accuracy 2 is the estimation accuracy for volume 2.

Table 2. Brain volumes with respective estimation accuracies for 10 Patients (Patient11 to Patient20) using Nanavati dataset.

Table 2 shows detailed results for next 10 patients (Patient11 to Patient20) using MRI volumetric data from Nanavati Hospital. Reference volumes are provided by doctors of Hospital. Volume 1 is the volume value estimated without using any filtering and volume refinement. Accuracy 1 is the estimation accuracy for volume 1. Filter column shows the name of filter applied. Volume 2 is the estimated brain volume after applying filter and volume refinement. Accuracy 2 is the estimation accuracy for volume 2.

Fig. 5: Graphs showing Brain volume estimation accuracies using OASIS data

Fig. 5 shows graphs of Brain volume estimation accuracies using Open Access Series of Imaging Studies (*OASIS*) dataset. It can be clearly interpreted that proposed model with GMI filtering performs the best.

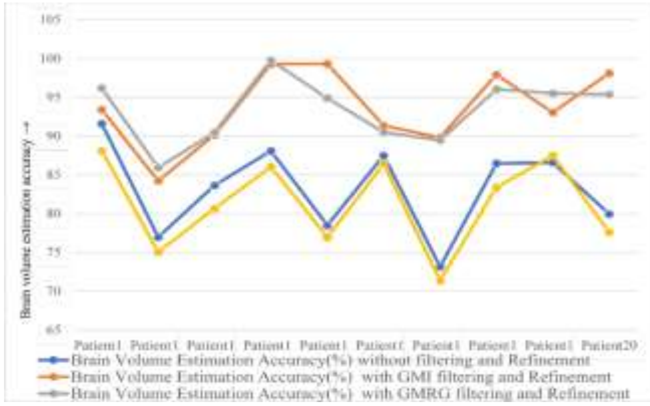

Fig. 6: Graphs showing Brain volume estimation accuracies using data from Nanavati Hospital

Fig. 6 shows graphs of Brain volume estimation accuracies using Nanavati dataset. From graphs it can be interpreted that proposed model with GMI and GMRG filtering gives comparable results.

5. Conclusion

On OASIS dataset, the proposed model performs best with GMI filter as compared to other filters with an average accuracy of 94.156%. Average estimation accuracies found using GMRG and GAD filtering and refinement are 90.52% and 82.09% respectively. After applying GMI and GMRG filtering and volume refinement, 11.68% and 8.04% increase in volume estimation accuracy is observed respectively while using GAD filtering average decrease of 0.38% is observed.

On Nanavati dataset, the proposed model gives comparable average accuracies using GMI and GMRG filters as 93.65% and 93.40% respectively. Average estimation accuracy found using and GAD filtering and refinement is 81.3%. After applying GMI and GMRG filtering and volume refinement, 10.41% and 10.16% increase in volume estimation accuracy is observed respectively while using GAD filtering average decrease of 1.94% is observed.

6. Conflicts of interest

The authors declare that they have no competing interest.

References

[1] S. Kobashi, N. Kamiura, Y. Hata, and M. Ishikawa, "Automatic Robust Threshold Finding Aided by Fuzzy Information Granulation," Oct. 1997. doi: 10.1109/ICIP.1997.648020.

[2] Y. Hata; S. Kobashi; S. Hirano; H. Kitagaki; E. Mori, "Automated segmentation of human brain MR images aided by fuzzy information granulation and fuzzy inference", doi: 10.1109/5326.885120.

[3] Tao Song; Mo M. Jamshidi; Roland R. Lee; Mingxiong Huang, "A Modified Probabilistic Neural Network for Partial Volume Segmentation in Brain MR Image", doi: 10.1109/TNN.2007.891635.

[4] Smitha Sunil Kumaran Nair; K. Revathy, "Quantitative Analysis of Brain Tissues from Magnetic Resonance Images." doi: 10.1109/ICDIP.2009.34.

[5] Stefan Bauer, Pascal P Gratz, Jan Gralla, Mauricio Reyes, Roland Wiest, "Towards automatic MRI volumetry for treatment selection in acute ischemic stroke patients." doi: 10.1109/EMBC.2014.6943891.

[6] Hassan Khastavaneh; Hossein Ebrahimpour-Komleh, "Brain extraction using isodata clustering algorithm aided by histogram analysis." doi: 10.1109/KBEI.2015.7436154.

[7] E. D. Bigler and D. F. Tate, "Brain Volume, Intracranial Volume, and Dementia:," *Invest. Radiol.*, vol. 36, no. 9, pp. 539–546,

Sep. 2001, doi: 10.1097/00004424-200109000-00006.

[8] J. Tohka, A. Zijdenbos, and A. Evans, “Fast and robust parameter estimation for statistical partial volume models in brain MRI,” *NeuroImage*, vol. 23, no. 1, pp. 84–97, Sep. 2004, doi: 10.1016/j.neuroimage.2004.05.007.

[9] K. Ishii *et al.*, “Automatic volumetric measurement of segmented brain structures on magnetic resonance imaging,” *Radiat. Med.*, vol. 24, no. 6, pp. 422–430, Aug. 2006, doi: 10.1007/s11604-006-0048-8.

[10] S. Mehta, T. J. Grabowski, Y. Trivedi, and H. Damasio, “Evaluation of voxel-based morphometry for focal lesion detection in individuals,” *NeuroImage*, vol. 20, no. 3, pp. 1438–1454, Nov. 2003, doi: 10.1016/S1053-8119(03)00377-X.

[11] “RP-Net: A 3D Convolutional Neural Network for Brain Segmentation From Magnetic Resonance Imaging”, doi: 10.1109/ACCESS.2019.2906890.

[12] Henrike Wolf,Per Julin,Hermann-Josef Gertz,Bengt Winblad,Lars-Olof Wahlund, “Intracranial volume in mild cognitive impairment, Alzheimer’s disease and vascular dementia: evidence for brain reserve?”, doi: https://doi.org/10.1002/gps.1205.

[13] Karen J. Ferguson PhD,Joanna M. Wardlaw FRCR, FRCPE,C. Louise Edmond BSc, MB, ChB,Ian J. Deary PhD, FRCPE, FRSE,Alasdair M. J. MacLullich MRCP, PhD, “Intracranial Area: A Validated Method for Estimating Intracranial Volume”, doi: https://doi.org/10.1111/j.1552-6569.2005.tb00289.x.

[14] J. Eritaia *et al.*, “An optimized method for estimating intracranial volume from magnetic resonance images,” *Magn. Reson. Med.*, vol. 44, no. 6, pp. 973–977, Dec. 2000, doi: 10.1002/1522-2594(200012)44:6<973::AID-MRM21>3.0.CO;2-H.

[15] I. Driscoll *et al.*, “Longitudinal pattern of regional brain volume change differentiates normal aging from MCI,” *Neurology*, vol. 72, no. 22, pp. 1906–1913, Jun. 2009, doi: 10.1212/WNL.0b013e3181a82634.

[16] Saman Sargolzaei 1, Arman Sargolzaei 1, Mercedes Cabrerizo 1, Gang Chen 2, Mohammed Goryawala 1, Alberto Pinzon-Ardila 3, Sergio M Gonzalez-Arias 3 4, Malek Adjouadi, “Estimating Intracranial Volume in Brain Research: An Evaluation of Methods”, doi: 10.1007/s12021-015-9266-5.

[17] N. Klasson, E. Olsson, C. Eckerström, H. Malmgren, and A. Wallin, “Estimated intracranial volume from FreeSurfer is biased by total brain volume,” *Eur. Radiol. Exp.*, vol. 2, no. 1, p. 24, Dec. 2018, doi: 10.1186/s41747-018-0055-4.

[18] Ridgway, GR; Barnes, J; Pepple, T; Fox, N;, “Estimation of total intracranial volume - a comparison of methods”, [Online]. Available: https://discovery.ucl.ac.uk/id/eprint/1315736

[19] Richard Norden, skjölda Filip et. al. “Intracranial volume estimated with commonly used methods could introduce bias in studies including brain volume measurement”, doi: https://doi.org/10.1016/j.neuroimage.2013.06.068.

[20] W. Xue, L. Zhang, X. Mou, and A. C. Bovik, “Gradient Magnitude Similarity Deviation: A Highly Efficient Perceptual Image Quality Index,” *IEEE Trans. Image Process.*, vol. 23, no. 2, pp. 684–695, Feb. 2014, doi: 10.1109/TIP.2013.2293423.

[21] C. Beitone, X. Balandraud, D. Delpueyo, and M. Grédiac, “Heat source reconstruction from noisy temperature fields using a gradient anisotropic diffusion filter,” *Infrared Phys. Technol.*, vol. 80, pp. 27–37, Jan. 2017, doi: 10.1016/j.infrared.2016.11.003.

[22] "Gradient Adaptive Image Restoration and Enhancement." Doi: doi:10.1109/icip.2006.313034.

[23] X. Zhang and X. Feng, "Hybrid gradient-domain image denoising," *AEU - Int. J. Electron.Commun.*, vol.68, no. 3, pp. 179–185, Mar. 2014, doi: 10.1016/j.aeue.2013.08.009.

[24] A. C. da Silva Senra Filho, F. H.Simozo, and L. O. M. Junior, "Brain volume refinement (BVeR):automaticcorrection tool as an alternative to manual intervention on brain segmentation," *Res. Biomed.Eng.*, vol. 37, no. 4, pp. 631–640, Dec. 2021, doi: 10.1007/s42600-021-00168-x.

[25] D. S. Marcus, A. F. Fotenos, J. G. Csernansky, J. C. Morris, and R. L. Buckner, "Open Access Series of Imaging Studies: Longitudinal MRI Data in Nondemented and Demented Older Adults," *J. Cogn.Neurosci.*, vol. 22, no. 12, pp. 2677–2684, Dec. 2010, doi: 10.1162/jocn.2009.21407.

[26] A. Fedorov *et al.*, "3D Slicer as an image computing platform for the Quantitative Imaging Network,"*Magn. Reson. Imaging*, vol. 30, no. 9, pp. 1323–1341, Nov. 2012, doi: 10.1016/j.mri.2012.05.001.