REVIEW ARTICLES

Magnetic resonance imaging based volumetry: a primary approach to unravelling the brain*

Huang Xiaoqi[1,2], Lü Su[1], Li Dongming[1] and Gong Qiyong[1,3]**

(1. Huaxi MR Research Centre (HMRRC), and Department of Radiology, West China Hospital / West China School of Medicine, Chengdu 610041, China; 2. Department of Psychiatry, West China Hospital / West China School of Medicine, Chengdu 610041, China; 3. Division of Medical Imaging, Faculty of Medicine, University of Liverpool, United Kingdom)

Accepted on January 1, 2007

Abstract Magnetic resonance (MR) imaging based volumetry is recognized as an important technique for studying the brain. In this review, two principle volumetric methods using high resolution MR images were introduced, namely the Cavalieri method and the voxel based morphometry (VBM). The Cavalieri method represents a manual technique that allows the volume of brain structures to be estimated efficiently with no systematic error or sampling bias, whereby the VBM represents an automated image analysis which involves the use of statistical parametric mapping of the MR imaging data. Both methods have been refined and applied extensively in recent neuroscience research. The present paper aims to describe the development of methodologies and also to update the knowledge of their applications in studying the normal and diseased brain.

Keywords: MR imaging, Cavalieri method, voxel-based morphometry, brain, volumetry.

Magnetic resonance (MR) is well established as a superior imaging modality for providing the anatomical and morphological information, and this is increasingly of importance in basic and clinical neuroscience. It is assumed that MR imaging based measure of the volume of a particular brain structure in healthy brain is partially determined by the number and size of the neurons it contains. Thus, greater volumes should mean that a structure works more efficiently[1]. Accordingly, it is plausible to hypothesize that, unless greater volume primarily reflects inadequate pruning of neurons in development[2] and other factors (such as the efficiency of neurotransmission) are fairly constant, individuals with larger brain regions should perform the functions mediated by those regions better. Therefore, with the superior image resolution in conjunction with the novel methods of volumetric image analysis, MR imaging based volumetry has become one of the most commonly used techniques in brain study. It provides a powerful non-invasive tool for accessing the change of the regional brain volume *in vivo*, and offers basic information for revealing the links between morphology, metabolism and function in both normal and diseased brain.

A T1-weighted three-dimensional (3D) MR technique is typically used to obtain anatomical high-spatial-resolution images, and normally, images acquired with conventional 1.5T MR scanners and 1 mm^3 voxels provide sufficient structural details. In addition, the widely available 3.0 T scanners now offer better image resolution with the advantage of short acquisition time. For commercial MR scanners, this technique is usually referred to as MP-RAGE (Siemens Medical Systems, Erlangen, Germany), 3D Fast SPGR (GE Healthcare, Milwaukee, Wisconsin, USA) or 3D TFE (Philips Medical Systems, Best, Netherlands). Traditionally, the brain structures are manually outlined on all contiguous slices where the regions of interest are evident[3], and volumes are usually calculated in cubic millimeters taking into account the size and the number of voxels within the outlined region. A number of computer-assisted techniques have been developed to provide fast, objec-

* Supported by National Natural Science Foundation of China (Grant Nos. 30625024, 30530300), the programs for NCET in University (Grant No. 04-0866), SRFDP (Grant No. 20060610073) and SRF for ROCS (Grant No. 2005383-10-5) from SEM, the Distinguished Young Scholars of Sichuan (Grant No. 05ZQ026-031), and the UK Royal Society International Joint Project with NSFC.

** To whom correspondence should be addressed. E-mail: cjr.gongqiyong@vip.163.com

tive, and precise volume quantification for brain structures. The accuracy and reproducibility of these techniques depend on the MR imaging sequence, the slice thickness, the degree of manual intervention, and the techniques utilized themselves[4]. In this article, we focus on the predominant methods of brain volumetric quantification based on MR imaging, i.e. the Cavalieri method and the voxel-based morphometry (VBM). Our goal is to review the development of the methodologies, capabilities and limitations of brain volumetric quantification, and to discuss their recent applications in neuroscience.

1 Cavalieri method

The Cavalieri method represents one of the new tools of modern stereology which can be defined as the statistical inference of geometrical parameters such as volumes and surface areas using sampled information[5]. When adapted and applied to MR data, the Cavalieri method of MR volumetry provides a mathematically unbiased method for determining structural volumes with high efficiency and precision[6], and it has the advantage of higher efficiency over conventional planimetry[7]. This approach involves two stage sampling of the MR imaging data as follows: stage one involves sectioning of the gross structure of interests on images. An object of interest is sectioned systematically with a series of parallel planes. A uniform, random start is required for the first section. Consecutive sections are acquired at equal intervals exhaustively through the object[5]. Systematic sampling has been shown to be more efficient than random sampling by a factor equal to the square root of the number of sections[8]. Only ten systematic sections are required to obtain the same precision as 100 random sections. By measuring the area of the structural profiles on each section, structural volume can then be estimated as the summation of the section areas multiplied by the distance between successive planes. The volume of the estimated object can be then defined as

$$\mathrm{est}_1 V = T(A_1 + A_2 + \cdots + A_m) \quad (\mathrm{cm}^3) \quad (1)$$

where $\mathrm{est}_1 V$ is an unbiased estimator of V, m is the number of sections and A_1, A_2, $\cdots$, A_m are the corresponding total transect areas on the m sections, and T is the distance between the parallel section images.

Stage two involves the point-counting which requires systematic sampling prior to estimating the cross-sectional area. Point-counting employs a test system comprising a systematic array of points in a uniform random position which can be overlaid on the sectional images of an object of interest[6, 9, 10]. This test system has been incorporated into several software packages (e.g. ANZLYZE image software (MAYO Foundation, Minnesota, USA) which can be applied at ease on any computer workstation. The starting position of the test system is uniformly random. No preferred start position for point counting should be allowed in order to ensure the unbiased nature of the method[11]. The number of test points falling within the section profile is counted. The total section area can then be estimated by

$$\mathrm{est}A_i = (a/p) \cdot M^{-2} \cdot P_i \quad (i = 1, 2, \cdots, m) \quad (2)$$

where $\mathrm{est}A_i$ is an unbiased estimate of sectional area (cm^2), (a/p) is the test area associate with each test point (cm^2), namely $d^2(\mathrm{cm}^2)$ if a square grid is applied with a distance d cm between test points, and M is the linear magnification.

The unbiased volume estimator becomes

$$\mathrm{est}_2 V = T\frac{a}{p}(P_1 + P_2 + \cdots + P_m) \quad (\mathrm{cm}^3) \quad (3)$$

where $\mathrm{est}_2 V$ is an unbiased estimate of feature section area (cm^2), T is the distance between parallel planes (cm), $P_1, P_2, \cdots, P_m$ represent the point counts and a/p is the test area per test point (cm^2). The subscript "2" in $\mathrm{est}_2 V$ indicates that the volume is estimated by a two stage sampling, namely sectioning and point counting. To ensure that the total number of points counted is about 150, the distance d can be calculated by

$$d = \sqrt{V/(150T)} \quad (4)$$

where V is a rough guess of the volume (cm^3). i.e. if $V \approx 200\ \mathrm{cm}^3$, and $T = 3$ cm, then $d \approx 0.67$ cm. Counting more points will not add a significant precision to $\mathrm{est}_2 V$. In general, the best approach to increasing the precision of $\mathrm{est}_2 V$ is to reduce T (or increase the number of sections) instead of increasing the number of points to be counted.

The precision of a volume estimate made with the Cavalieri method cannot be assessed via usual statistical method as the cross-sectional areas on sequential slices are not independent quantities. Therefore, based on the theory of Matheron[12], new methods of

error predictions were developed taking into account the influence from the missing information between sections and point-counting[8, 13]. Point counting contributes to the variance in two ways: it produces uncertainty with respect to the measures of section area, and it produces uncertainty with respect to the differences between sections. Calculation of these contributions involves the dimensionless shape coefficient[14]. For a specific object, the relevant shape coefficient is relatively constant for a chosen sampling direction, and it is usually sufficient to estimate this coefficient only once in a pilot study.

The Cavalieri method ideally should be applied in infinitely thin sections[8]. However, given that the slice thickness selected is small (as a rule of thumb, smaller than 1/10 of the total length along the sampling direction), the Cavalieri estimator of volume will be practically unbiased. A worked example in a patient with multiple sclerosis is illustrated in Fig. 1. To estimate the cerebellar volume, the same systematic random sagittal sections are shown in the two rows, each separated by a distance of 17 images (slice thickness = 0.14 cm), which corresponds to a distance, T, of 2.39 cm. By counting intersections (yellow cross) with the square grid of test lines (red) overlaid on the tumour sections in the top row of Fig. 1, the volume of the tumour is estimated to be 4.16. In the bottom row of Fig. 1, the same sections are overlaid with a test system and the point counting was performed using a square grid size of 15 pixels, which is equivalent to 2.15 cm. The number of points recorded as lying in cerebellum on consecutive sections is 11, 33, 34, 37 and 11, which gives a total of 126. An unbiased estimate of the cerebellar volume therefore is $126 \times 2.145767 \times 2.39 = 646.69$ cm^3. The predicted coefficient error on the volume estimate obtained is 2.7% using the optimized formula[8, 15].

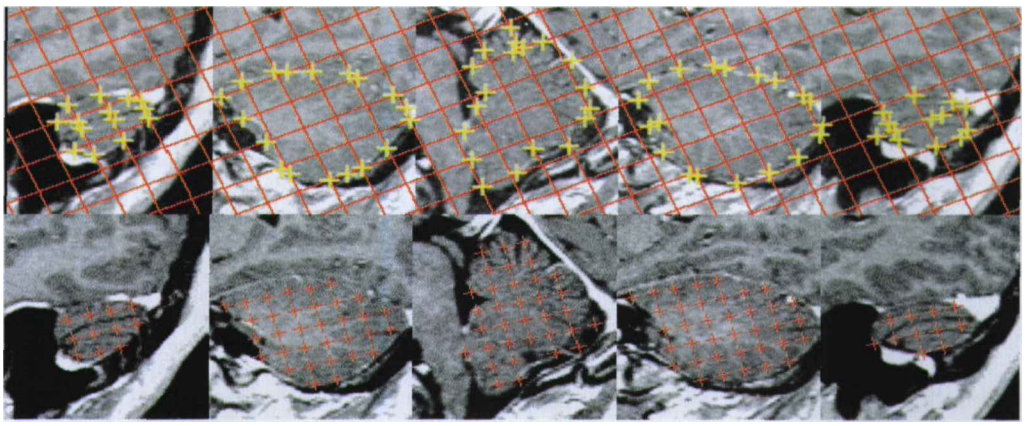

Fig. 1. Illustration of the application of Cavalieri method in the estimation of cerebellar volume. The same systematic random sagittal sections are shown in the two rows. In the first row, the images are overlaid with a square grid suitable for obtaining estimates of the dimensionless shape coefficient by point and intersection counting; in the second row, the images are overlaid with a test system for point counting. Details of the calculation of the volume and precision are given in the text.

Introduction of the Cavalieri method to the MR volumetry undoubtedly provides an important quantitative measure in clinical neuroscience. These include estimation of the total fetal brain volume in one of the early studies of intrauteral growth retardation[10]. In this study, the first MR imaging evidences were obtained to support the theory of brain sparing in the abnormal fetus which was thought to be the result of unfavorable effects on growth that occur in early pregnancy. In the study of multiple sclerosis, based on the original work by Gong et al.[16], Edwards et al. presented the volumetric data for the brainstem, cerebellum and upper cervical cord in a cross-sectional study[15]. A relatively moderate relationship was demonstrated between clinical disability and upper cervical cord volume (C1-C3) obtained from 3D MR images. In this study, the predicted coefficient error of better than 6% can be achieved when counting 100 to 200 points on 6 to 9 systematic sagittal sections through each infratentorial structure and the volume estimation for each infratentorial structure can be accomplished by an experienced user in less than 5 minutes. The Cavalieri method was also applied in patients with epilepsy[17], chronic substance abuse[18] and animal studies[19, 20].

As one of the practical methods of MR volumetry, the application of the Cavalieri method is evolv-

ing[20,21]. Subject to the individual structure of interests in normal or abnormal condition, the method itself has been constantly optimized, and the high efficiency of the method for volume estimation has been demonstrated[9—11,15,22,23]. To improve the precision of volume estimation for certain brain structures with circular shape, the Cavalieri method can be further developed based on the Pappus method of modern design stereology[24]. Fornix, for instance, is one of such structures of interests in psychological research. It has long been controversial as to what extent the fornix contribute to memory[25], and there is no objective method to assess its volume in normal and lesion studies. Whereas estimation of volume by the Cavalieri method employs linear sectioning, the Pappus method employs co-axial sectioning[24]. The former is particularly appropriate for estimating volume of the elongate object. For the fornix the Pappus method is ideal since, if viewed on sagittal sections, the fornix tracks in an anteriorly facing semi-circle in its path from the hippocampus to the anterior column. In a small cohort study of patients with impaired memory, Gong et al.[26] first implemented the Pappus method on 3D high resolution MR images and provided the volumetric data of the fornix which allow the fornix thinning to be detected in patients with organic amnesia.

Another feature of the Cavalieri method is that it permits convenient assessment of volumetric changes in the brain tissue integrity. In conjunction with the MR parametric mapping techniques, it provides a unique opportunity to quantify regions which are difficult to measure by conventional MR imaging methods. The refined method has recently been developed by Gong et al.[23] in the study of brain tumor after radiotherapy in an attempt to monitor volumetric changes of the abnormal brain tissues adjacent to tumour on 3D MR images obtained at fortnightly intervals in patients with high grade glioma. The volumes of interests were defined as, first, the enhancing abnormality which was the portion of tumour on 3D post-contrast T1-weighted image within the enhancement boundary, and secondly, the non-enhancing abnormality which is the abnormalities observed on T2 and magnetization transfer ratio (MTR) tissue characterization maps surrounding regions of tumour enhancement. As illustrated in Fig. 2, the volumes of non-enhancing abnormalities can be readily obtained, which is not possible with the use of the conventional technique, and it was recommended for the objective assessment of tumour response to the therapeutic intervention.

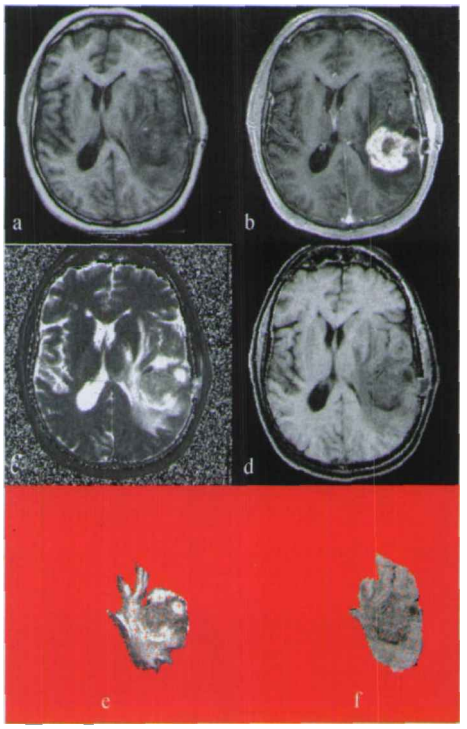

Fig. 2. Example images for assessing volumetric changes of the impaired brain integrity in a patient with glioma. (a) Pre-contrast T1 weighted image; (b) post-contrast T1 weighted image; (c) T2 map; (d) magnetization transfer ratio (MTR) map. T2 map (e) and MTR map (f) are red colour-coded so that the total abnormality can be readily identified within the coloured region. Note that stereological test systems for point counting are overlaid on enhancing abnormality (top right panel), T2 total abnormality (bottom left panel), and MTR total abnormality (bottom right panel) with uniform random position for volume estimation. Each red cross (+) signifies one test point.

2 Voxel based morphometry

Voxel-based morphometry (VBM) is another commonly used technique of MR volumetry[27]. The number of publications with the use of VBM is fast growing. This method involves the segmentation of MR images into different tissue types (e.g. grey matter, white matter, and cerebrospinal fluid) and produces the statistical parametric maps of imaging data. The grey or white matter map resulting from segmentation represents the spatial distribution for each individual at the level of every voxel. This method allows the quantification of group differences without any priori region-of-interest, and it is freely available in popular software packages such as SPM (Welcome Department of Imaging Neuroscience, London, UK) and FSL (FMRIB Analysis Group, Oxford, UK). However, as MR images need to be

registered to the same stereotactic space as a priori images, the segmentation is prone to registration errors. Various methods have been developed to improve registration accuracy, such as employing segmented images for registration[28], a mixed model of registration, tissue classification, and bias correction[29], and utilizing the high-resolution registration techniques[30].

A modified version of VBM, the so-called optimized VBM, was developed by Good et al.[28] and was subsequently widely applied[31—33]. It minimizes the inherent problems of the brain artifact resulting from the non-brain tissues when utilizing the conventional VBM method. This method involves a number of spatial transformation steps prior to voxel-wise statistical analysis. Routinely, grey/white matter was automatically segmented from the raw MR images using tissue signal intensity values and a priori information about the distribution of brain tissue type (the 148 normal dataset of the Montreal Neurological Institute). An automated brain extraction step was employed to eliminate the voxels from non-grey matter structures, such as the dural venous sinuses, scalp, cranial marrow, and diploic space, which are inherently included as brain tissue during standard segmentation due to similar voxel intensities as grey matter. Grey matter partitions were then spatially normalized (usually using a 12-parameter affine transformation and $7 \times 8 \times 7$ non-linear basis functions as the default normalization parameters) to a customized grey matter template, which was constructed from the normalized, segmented and smoothed grey matter datasets of all studying subjects. The deformation parameters obtained from the normalization process were applied to the original raw images (in native space) of all participants to create optimally normalized whole-brain images, which were recursively segmented and the brain tissue was extracted. The optimally processed images were smoothed with an isotropic Gaussian kernel, size of which is dependent on the volume of brain structure of interests, e.g. using full width-half maximum of 8 mm for prefrontal cortex[33]. Voxel-wise statistical analyses on these data provide statistical parametric maps of grey or white matter. The output for the analysis is a statistical parametric map of the t statistic (SPM$\{t\}$), which can be transformed to a normal distribution (SPM $\{z\}$). Subject to the valid prior hypothesis, brain regions with significance from analyses are usually thresholded at a p value of less than 0.05 (corrected for multiple comparisons).

With respect to probing the normal brain, VBM method has been used to study the effect of some factors such as handedness[34,35], intelligence[33,36], age[28,37,38], gender[39,40] and personality[41] on brain. The plasticity of the brain has also been demonstrated structurally in the studies of musicians[42,43], taxi drivers[44] and speech sound production[45,46]. It was also found that there were grey matter changes in healthy individuals dependent on training in comparison to controls[47,48]. Particularly, a significant increase in grey matter was reported for jugglers induced by a 3-month training[47], and interestingly, the volume of the grey matter reduced to the original volume after training stopped. In an attempt to explore the genotype effects on brain, recent VBM studies have indicated that the polymorphism of certain genes[49,50] might cause the structural alterations.

A recent study by Gong et al.[33] reported the use of MR imaging based volumetry by combining the Cavalieri method and VBM to investigate the relationship of the human intelligence with brain structures. The prefrontal cortical subfield volumes were specifically assessed in conjunction with the use of a previously established parcellation technique[51]. To facilitate the analysis, the 3D MR dataset was parcellated based on macroanatomical landmarks. The procedure involved resizing the dataset to isotropic voxels, reformatting the image, and orienting it to a standardised sagittal plane orthogonal to the bicommissural plane. Within each hemisphere, prefrontal cortex was divided into four subfields, namely dorsolateral, dorsomedial, orbitolateral and orbitomedial areas in consistent with Damasio's anatomical demarcations[52]. These subfields are relevant to the functional subdivisions of prefrontal cortex supported by neuropsychological, neuropsychiatric and neuroimaging studies[51,53]. Total intracranial volumes were also estimated and used as a basis for normalising the regional brain volumes by applying the method as described by Gong et al.[15,16]. The Cavalieri volume estimates of the prefrontal subfields were correlated with neuropsychological measures of fluid intelligence by performing a stepwise multiple regression analyses. The author concluded that the medial aspect of

prefrontal cortex plays an important role in mediating human intellectual performance, converging with the findings from the VBM (Fig.3). The convergent evidence obtained from this study represents important methodological cross-validation of the significance of medial prefrontal cortex in human intelligence.

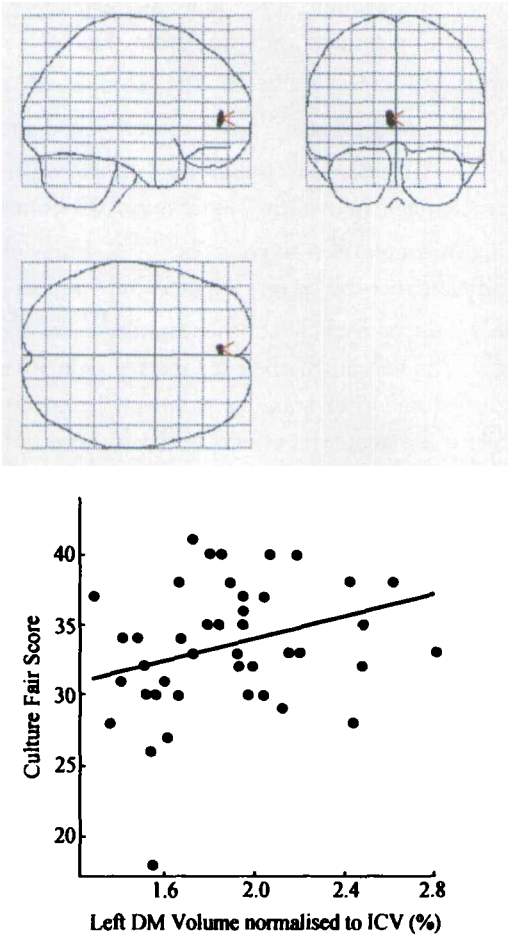

Fig. 3. Statistical parametric maps (top panel) showing a positive correlation between grey matter and Culture Fair scores. A single cluster in the medial region of frontal cortex shows a significant positive correlation between Culture Fair scores and grey matter ($p<0.05$ corrected for the multiple comparisons). The red cursors (<) point to the locations of the global maxima. Results of stereological analysis for left dorsomedial (DM) prefrontal cortex support this finding (bottom panel). The multi-covariate regression analysis of prefrontal left DM volume was expressed as percentage fractions of intracranial volume (ICV) against Culture Fair Scores with fitted regression line ($\beta=0.50$, $p<0.05$).

The application of VBM has been increasingly extended for the investigation of the neuropsychiatric diseases in recent years. This includes posttraumatic stress disorder[54], alcoholics[55], eating disorder[56], headache[57,58], tinnitus[59], amusia[60], aphasia[61], autism[62], mild cognitive impairment[63], bipolar disorder[64], narcolepsy[65,66], Tourette's syndrome[67], Alzheimer's disease[63,68], epilepsy[69,70], Parkinson's disease[71,72], multiple sclerosis[73,74], and the literature is still fast growing. Notably, amongst all VBM studies schizophrenia is particularly of interest[75—80]. A recent review by Honea et al.[81] has reported the regional defects in brain volume of schizophrenia in a meta-analysis of VBM studies, with the inclusion of 15 studies recruiting a total of 390 schizophrenic patients and 364 healthy volunteers. This is also evident in the recent studies of the first episode, treatment naive schizophrenia patients reported by a research team from China[82—84]. For instance, a disassociation of the global grey/white matter ratio with age was found, and this supports the notion that there may be an impaired balance of grey and white matter in patients with schizophrenia[82]. Additionally, by taking the approach of VBM and applying the methodology to diffusion tensor imaging and magnetization transfer data, Huang et al.[83,84] reported the gender difference with respect to the brain abnormalities in first-episode schizophrenia in addition to distinguishing early and adult onset schizophrenia in first episode drug-naive patients. Furthermore, recent study of refractory depression by Yang et al.[85] has revealed the brain abnormalities using the similar approach, and study of epilepsy by Lui et al.[69] reported white matter abnormalities beyond epileptogenic zone in patients with normal appearing brain on conventional MR imaging.

3 Limitation and future aspect

Common to any volumetric analysis on MR imaging data, the results from the Cavalieri method or VBM depend on the quality of MR images. Any technical advances in increasing the resolution of MR images will improve the results of the volumetric analysis. Image artifacts, such as partial volume effect, chemical shift and susceptibility, cause difficulty in determining the true boundary of the region of interest and hence contribute to error of volumetry. However, with the development of the new MR sequences, this difficulty has largely been overcome by the acquisition of the 3D high-resolution MR images. When acquiring data from a living subject by MR imaging, any random movement such as twitching and tremor, can result in image artifact which can be minimized with the use of fast MR imaging techniques. Furthermore, the use of the advanced pulse sequences additionally detects subtle changes in the cortex that are difficult to detect on conventional MR

imaging scans[70]. For instance, 3D T1-weighted MDEFT sequence designed by Deichmann et al.[86] was recommended for structural analysis of its improved contrast between grey and white matter, and also for obtaining multi-slice co-registered series of T1-, T2- and PD-weighted images to support improved tissue classification[33]. The utilization of the high-field MR scanners certainly offers superior image resolution[87], and with its clinical availability, the 3.0T MR scanners have been increasingly used for the studies in clinical neuroscience[69,82—85].

However, issue remains with respect to effectively comparing or combining the MR dataset from different research institutions. This is due to the site-specific properties attributed to MR scanners in different research institutions[88]. Unless this is resolved, MR imaging based volumetry will be difficult to serve as a robust tool for multi-center study of the brain diseases. Further issue arising from the MR imaging based volumetry involves the variation in the measured volumes among individuals. This is apparent as most studies were carried out for small patient samples in a cross-sectional manner. For the Cavalieri method, this is attributed to both the inherent biological variance among the measured volumes and the precision of the individual volume estimates. Gong et al.[16] took the measure of normalizing the regional volume to the total intra-cranial volume for each individual for minimizing this effect, and this is subsequently applied in patients with multiple sclerosis[15] and in the study of brain structural correlation with the human intellectual performance[33]. Additionally, the result of the Cavalieri method is also susceptible to observer dependent interpretation of images[89]. For VBM, this inter-subject variance can be largely removed by application of image normalization step. Nevertheless, the ideal approach to resolving this issue is to investigate the volume changes of the individual brain overtime by using the identical MR imaging protocol. The resulting images can be matched to each other taken at different time points during the course of the longitudinal study, and this is reported to be highly sensitive to reveal the subtle changes which cannot be detected in cross-sectional studies[16,47].

Currently, the interpretation of the brain abnormalities detected by MR imaging based volumetry must take precaution before exactly knowing whether these are the causes of or the results of the disease[90]. In addition, neuronal substrate underlying such volumetric changes remains unanswered, and this issue could not be addressed unless the histological data is available for comparison. Lesion studies, however, may shed light on the underlying mechanism of the brain[25,91]. As MR imaging technique enables the multi-mode approaches for probing brain by providing the structural, functional and metabolic information, the observed volumetric deficit can be cross-validated by combining MR imaging based volumetry, functional neuroimaging techniques and MR spectroscopy. Methodological cross-validation (i.e. the combined use of at least two methods)[33,92] could also be applied to provide convergent results to support the findings so as to improve our understanding of the brain.

4 Summary

As the main methods of MR imaging based volumetry, both Cavalieri method and VBM are improving, and they have been popularly used to explore the normal and diseased brain. This is largely due to technical advances in MR imaging techniques as well as in the volumetric methods themselves. However, both methods have their pros and cons, and they cannot serve as a substitute for each other[93]. In addition, the clinical relevance of the volumetric changes detected is still not known. It is recommended to cross-validate the findings by combining different volumetric methods. In particular, by taking the advantage of the multi-mode MR imaging modalities of acquiring the structural, functional and metabolic information as reported in our most recent studies[94,95], MR imaging based volumetry will become a powerful tool to unravel the brain, and clinically to provide useful biomarkers for early diagnosis and monitoring progression of the brain diseases.

Acknowledgement The authors gratefully acknowledge the support from the Magnetic Resonance and Image Analysis Research Centre (MARIARC) of the University of Liverpool, UK. Dr. Gong also acknowledges his appointment as the UK University Honorary Fellow in the Division of Medical Imaging, Faculty of Medicine, the University of Liverpool, UK.

References

1 Andreasen NC, Flaum M, Swayze V, et al. Intelligence and brain structure in normal individuals. Am J Psychiatry, 1993, 150(1): 130—134

2 Howard MA, Cowell PE, Boucher J, et al. Convergent neuroanatomical and behavioural evidence of an amygdala hypothesis of autism. Neuroreport, 2000, 11(13): 2931—2935

3 Jack CR, Bentley MD, Twomey CK, et al. MR imaging-based volume measurements of the hippocampal formation and anterior temporal lobe: validation studies. Radiology, 1990, 176(1): 205—209

4 Simon JH, Scherzinger A, Raff U, et al. Computerized method of lesion volume quantitation in multiple sclerosis: error of serial studies. AJNR Am J Neuroradiol, 1997, 18(3): 580—582

5 Weibel ER. Practical methods for biological morphometry. In: Stereological Methods. London: Academic Press, 1979; 237—256

6 Roberts N, Cruz-Orive LM, Reid NM, et al. Unbiased estimation of human body composition by the Cavalieri method using magnetic resonance imaging. J Microsc, 1993, 171(Pt 3): 239—253

7 Cotter D, Miszkiel K, Al-Sarraj S, et al. The assessment of post-mortem brain volume; a comparison of stereological and planimetric methodologies. Neuroradiology, 1999, 41(7): 493—496

8 Gundersen HJ and Jensen EB. The efficiency of systematic sampling in stereology and its prediction. J Microsc, 1987, 147(Pt 3): 229—263

9 Gong QY, Phoenix J, Kemp GJ, et al. Estimation of body composition in muscular dystrophy by MRI and stereology. J Magn Reson Imaging, 2000, 12(3): 467—475

10 Gong QY, Roberts N, Garden AS, et al. Fetal and fetal brain volume estimation in the third trimester of human pregnancy using gradient echo MR imaging. Magn Reson Imaging, 1998, 16(3): 235—240

11 Gong QY, Tan LT, Romaniuk CS, et al. Determination of tumour regression rates during radiotherapy for cervical carcinoma by serial MRI: comparison of two measurement techniques and examination of intraobserver and interobserver variability. Br J Radiol, 1999, 72(853): 62—72

12 Matheron G. The Theory of Regionalised Variables and It's Applications. No.5. Fontainebleau, France: Ecole Nationale Superieure des Mines de Paris, 1971

13 Cruz-Orive LM. On the precision of systematic sampling: a review of Matheron's transitive methods. J Micros, 1989, 153: 315—333

14 Pache JC, Roberts N, Vock N, et al. Vertical sectioning and parallel CT scanning designs for stereology: application to human lung. J Microsc, 1993, 170: 3—24

15 Edwards SG, Gong QY, Liu C, et al. Infratentorial atrophy on magnetic resonance imaging and disability in multiple sclerosis. Brain, 1999, 122 (Pt 2): 291—301

16 Gong QY, Liu C, Edwards SG, et al. Serial study of infratentorial atrophy and disability in multiple sclerosis using 3D magnetic resonance imaging with stereology. Radiology, 1998, 209P: 241

17 Salmenpera T, Kononen M, Roberts N, et al. Hippocampal damage in newly diagnosed focal epilepsy: a prospective MRI study. Neurology, 2005, 64(1): 62—68

18 Schlaepfer TE, Lancaster E, Heidbreder R, et al. Decreased frontal white-matter volume in chronic substance abuse. Int J Neuropsychopharmacol, 2006, 9(2): 147—153

19 Redwine JM, Kosofsky B, Jacobs RE, et al. Dentate gyrus volume is reduced before onset of plaque formation in PDAPP mice: a magnetic resonance microscopy and stereologic analysis. Proc Natl Acad Sci USA, 2003, 100(3): 1381—1386

20 Johnson K, Ryan L, Davis J, et al. Application of magnetic resonance imaging in developmental neurotoxicity testing: a pilot study. Neurotoxicology, 2006, 27(5): 846—851

21 Garcia-Finana M, Cruz-Orive LM, Mackay CE, et al. Comparison of MR imaging against physical sectioning to estimate the volume of human cerebral compartments. Neuroimage, 2003, 18(2): 505—516

22 Gong QY, Brunt JN, Romaniuk CS, et al. Contrast enhanced dynamic MRI of cervical carcinoma during radiotherapy: early prediction of tumour regression rate. Br J Radiol, 1999, 72(864): 1177—1184

23 Gong QY, Eldridge PR, Brodbelt AR, et al. Quantification of tumour response to radiotherapy. Br J Radiol, 2004, 77(917): 405—413

24 Cruz-Orive LM and Roberts N. Unbiased volume estimation with coaxial sections: an application to the human bladder. J Microsc, 1993, 170(Pt 1): 25—33

25 Aggleton JP, McMackin D, Carpenter K, et al. Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. Brain, 2000, 123(Pt 4): 800—815

26 Gong QY, Montaldi D, Mayes AR, et al. A new efficient and unbiased method for estimation of fornix and hippocampal volume on co-axial MR images. Neuroimage, 2001, 13(6): S131

27 Ashburner J and Friston KJ. Voxel-based morphometry—the methods. Neuroimage, 2000, 11(6 Pt 1): 805—821

28 Good CD, Johnsrude IS, Ashburner J, et al. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage, 2001, 14(1 Pt 1): 21—36

29 Ashburner J and Friston KJ. Unified segmentation. Neuroimage, 2005, 26(3): 839—851

30 Shen D and Davatzikos C. Very high-resolution morphometry using mass-preserving deformations and HAMMER elastic registration. Neuroimage, 2003, 18(1): 28—41

31 Ananth H, Popescu I, Critchley HD, et al. Cortical and subcortical gray matter abnormalities in schizophrenia determined through structural magnetic resonance imaging with optimized volumetric voxel-based morphometry. Am J Psychiatry, 2002, 159(9): 1497—1505

32 Karas GB, Burton EJ, Rombouts SA, et al. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage, 2003, 18(4): 895—907

33 Gong QY, Sluming V, Mayes A, et al. Voxel-based morphometry and stereology provide convergent evidence of the importance of medial prefrontal cortex for fluid intelligence in healthy adults. Neuroimage, 2005, 25(4): 1175—1186

34 Good CD, Johnsrude I, Ashburner J, et al. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage, 2001, 14(3): 685—700

35 Herve PY, Crivello F, Perchey G, et al. Handedness and cerebral anatomical asymmetries in young adult males. Neuroimage, 2006, 29(4): 1066—1079

36 Colom R, Jung RE and Haier RJ. Distributed brain sites for the g-factor of intelligence. Neuroimage, 2006, 31(3): 1359—1365

37 Lehmbeck JT, Brassen S, Weber-Fahr W, et al. Combining voxel-based morphometry and diffusion tensor imaging to detect age-related brain changes. Neuroreport, 2006, 17(5): 467—470

38 Tisserand DJ, van Boxtel MP, Pruessner JC, et al. A voxel-based morphometric study to determine individual differences in gray matter density associated with age and cognitive change over time. Cereb Cortex, 2004, 14(9): 966—973

39 Suzuki M, Hagino H, Nohara S, et al. Male-specific volume expansion of the human hippocampus during adolescence. Cereb Cortex, 2005, 15(2): 187—193

40 Van Laere KJ and Dierckx RA. Brain perfusion SPECT: age- and sex-related effects correlated with voxel-based morphometric findings in healthy adults. Radiology, 2001, 221(3): 810—817

41 Kaasinen V, Maguire RP, Kurki T, et al. Mapping brain structure and personality in late adulthood. Neuroimage, 2005, 24(2): 315—322

42 Bermudez P and Zatorre RJ. Differences in gray matter between musicians and nonmusicians. Ann N Y Acad Sci, 2005, 1060: 395—399

43 Luders E, Gaser C, Jancke L, et al. A voxel-based approach to gray matter asymmetries. Neuroimage, 2004, 22(2): 656—664

44 Maguire EA, Spiers HJ, Good CD, et al. Navigation expertise and the human hippocampus: a structural brain imaging analysis. Hippocampus, 2003, 13(2): 250—259

45 Golestani N and Pallier C. Anatomical Correlates of Foreign Speech Sound Production. Cereb Cortex, 2006, [Epub ahead of print]

46 Golestani N, Paus T and Zatorre RJ. Anatomical correlates of learning novel speech sounds. Neuron, 2002, 35(5): 997—1010

47 Draganski B, Gaser C, Busch V, et al. Neuroplasticity: changes in grey matter induced by training. Nature, 2004, 427(6972): 311—312

48 May A, Hajak G, Ganssbauer S, et al. Structural Brain Alterations following 5 Days of Intervention: Dynamic Aspects of Neuroplasticity. Cereb Cortex, 2006, [Epub ahead of print]

49 Kippenhan JS, Olsen RK, Mervis CB, et al. Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome. J Neurosci, 2005, 25(34): 7840—7846

50 Nemoto K, Ohnishi T, Mori T, et al. The Val66Met polymorphism of the brain-derived neurotrophic factor gene affects age-related brain morphology. Neurosci Lett, 2006, 397(1—2): 25—29

51 Gur RE, Cowell PE, Latshaw A, et al. Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. Arch Gen Psychiatry, 2000, 57(8): 761—768

52 Damasio H. Human Brain Anatomy in Computerized Images. New York: Oxford University Press, 1995

53 Gusnard DA, Akbudak E, Shulman GL, et al. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci USA, 2001, 98(7): 4259—4264

54 Yamasue H, Kasai K, Iwanami A, et al. Voxel-based analysis of MRI reveals anterior cingulate gray-matter volume reduction in posttraumatic stress disorder due to terrorism. Proc Natl Acad Sci USA, 2003, 100(15): 9039—9043

55 Fein G, Landman B, Tran H, et al. Brain atrophy in long-term abstinent alcoholics who demonstrate impairment on a simulated gambling task. Neuroimage, 2006, 32(3): 1465—1471

56 Wagner A, Greer P, Bailer UF, et al. Normal brain tissue volumes after long-term recovery in anorexia and bulimia nervosa. Biol Psychiatry, 2006, 59(3): 291—293

57 May A. Functional anatomy of headache. Neurol Sci, 2006, 27 (suppl 2): S103—106

58 May A, Ashburner J, Buchel C, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med, 1999, 5(7): 836—838

59 Muhlau M, Rauschecker JP, Oestreicher E, et al. Structural brain changes in tinnitus. Cereb Cortex, 2006, 16(9): 1283—1288

60 Hyde KL, Zatorre RJ, Griffiths TD, et al. Morphometry of the amusic brain: a two-site study. Brain, 2006, 129(Pt 10): 2562—2570

61 Josephs KA, Duffy JR, Strand EA, et al. Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain, 2006, 129(Pt 6): 1385—1398

62 Spencer MD, Moorhead TW, Lymer GK, et al. Structural correlates of intellectual impairment and autistic features in adolescents. Neuroimage, 2006

63 Stoub TR, deToledo-Morrell L, Stebbins GT, et al. Hippocampal disconnection contributes to memory dysfunction in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci USA, 2006, 103 (26): 10041—10045

64 Adler CM, Delbello MP, Jarvis K, et al. Voxel-Based Study of Structural Changes in First-Episode Patients with Bipolar Disorder. Biol Psychiatry, 2006

65 Brenneis C, Brandauer E, Frauscher B, et al. Voxel-based morphometry in narcolepsy. Sleep Med, 2005, 6(6): 531—536

66 Draganski B, Geisler P, Hajak G, et al. Hypothalamic gray matter changes in narcoleptic patients. Nat Med, 2002, 8(11): 1186—1188

67 Kassubek J, Juengling FD and Ludolph AG. Heterogeneity of voxel-based morphometry findings in Tourette's syndrome: an effect of age? Ann Neurol, 2006, 59(5): 872—873

68 Teipel SJ, Flatz WH, Heinsen H, et al. Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. Brain, 2005, 128(Pt 11): 2626—2644

69 Lui S, Li CX, Ouyang L, et al. Voxel based analysis of diffusion tensor imaging in temporal lobe epilepsy with normal appearing brain on MRI. Neuroimage, 2006, 31: S130

70 Rugg-Gunn FJ, Boulby PA, Symms MR, et al. Imaging the neocortex in epilepsy with double inversion recovery imaging. Neuroimage, 2006, 31(1): 39—50

71 Beyer MK, Janvin CC, Larsen JP, et al. An MRI study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel based morphometry. J Neurol Neurosurg Psychiatry, 2006

72 Summerfield C, Junque C, Tolosa E, et al. Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study. Arch Neurol, 2005, 62(2): 281—285

73 Prinster A, Quarantelli M, Orefice G, et al. Grey matter loss in relapsing-remitting multiple sclerosis: a voxel-based morphometry study. Neuroimage, 2006, 29(3): 859—867

74 Sepulcre J, Sastre-Garriga J, Cercignani M, et al. Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. Arch Neurol, 2006, 63(8): 1175—1180

75 Gurling HM, Critchley H, Datta SR, et al. Genetic association and brain morphology studies and the chromosome 8p22 pericentriolar material 1 (PCM1) gene in susceptibility to schizophrenia. Arch Gen Psychiatry, 2006, 63(8): 844—854

76 Ho BC, Milev P, O'Leary DS, et al. Cognitive and magnetic resonance imaging brain morphometric correlates of brain-derived neurotrophic factor Val66Met gene polymorphism in patients with schizophrenia and healthy volunteers. Arch Gen Psychiatry, 2006, 63(7): 731—740

77 Hulshoff Pol HE, Schnack HG, Mandl RC, et al. Gray and white matter density changes in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry. Neuroimage, 2006, 31(2): 482—488

78 Lymer GK, Job DE, William T, et al. Brain-behaviour relationships in people at high genetic risk of schizophrenia. Neuroimage, 2006, 33(1): 275—285

79 McIntosh AM, Job DE, Moorhead WJ, et al. Genetic liability to schizophrenia or bipolar disorder and its relationship to brain structure. Am J Med Genet B Neuropsychiatr Genet, 2006, 141(1): 76—83

80 Whitford TJ, Grieve SM, Farrow TF, et al. Progressive grey matter atrophy over the first 2—3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. Neuroimage, 2006, 32(2): 511—519

81 Honea R, Crow TJ, Passingham D, et al. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. Am J Psychiatry, 2005, 162(12): 2233—2245

82 Lui S, Ouyang L, Deng W, et al. Global gray/white matter ratio and gray matter volume reflect abnormal aging neurodevelopment in treatment naive schizophrenics. Proc. Intl. Soc. Mag. Reson. Med., 2006, 14: 2078

83 Huang XQ, Wang YQ, Lui S, et al. Magnetization Transfer Imaging in distinguishing Early and Adult Onset Schizophrenia in drug-naive first-episode patients. Proc. Intl. Soc. Mag. Reson. Med., 2006, 14: 2669

84 Huang XQ, Li C, Lui S, et al. Cerebral abnormalities in first-episode schizophrenia: Gender difference revealed by diffusion tensor imaging. Neuroimage, 2006, 31: S146

85 Yang H, Li C, Sun X, et al. A Diffusion Tensor Imaging Investigation of Refractory Depression Using 3T MR. In: Proceedings of the 92nd Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA)[Oral presentation]. Chicago, Illinois, USA, November 26—December 1, 2006

86 Deichmann R, Schwarzbauer C and Turner R. Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3 T. Neuroimage, 2004, 21(2): 757—767

87 Augustinack JC, van der Kouwe AJ, Blackwell ML, et al. Detection of entorhinal layer II using 7Tesla [correction] magnetic resonance imaging. Ann Neurol, 2005, 57(4): 489—494

88 Jovicich J, Czanner S, Greve D, et al. Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. Neuroimage, 2006, 30(2): 436—443

89 Jelsing J, Rostrup E, Markenroth K, et al. Assessment of in vivo MR imaging compared to physical sections in vitro—a quantitative study of brain volumes using stereology. Neuroimage, 2005, 26 (1): 57—65

90 Weiller C and Rijntjes M. Cluster headache: phrenology revisited? Nat Med, 1999, 5(7): 732—733

91 Yasuno F, Hirata M, Takimoto H, et al. Retrograde temporal order amnesia resulting from damage to the fornix. J Neurol Neurosurg Psychiatry, 1999, 67(1): 102—105

92 Douaud G, Gaura V, Ribeiro MJ, et al. Distribution of grey matter atrophy in Huntington's disease patients: A combined ROI-based and voxel-based morphometric study. Neuroimage, 2006, 32 (4): 1562—1575

93 Tisserand DJ, Pruessner JC, Sanz Arigita EJ, et al. Regional frontal cortical volumes decrease differentially in aging: an MRI study to compare volumetric approaches and voxel-based morphometry. Neuroimage, 2002, 17(2): 657—669

94 Zhou XL, Chen CS, Zang YF, et al. Dissociated brain organizations for single-digit addition and multiplication. NeuroImage, 2007, 35(2): 871—880

95 Yang H, Long XY, Yang YH, et al. Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI. NeuroImage, 2007, 36(1): 144—152