

Review article

# MRI-based brain volumetrics: emergence of a developmental brain science

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## Abstract

MRI-based brain volumetrics is an established methodology of great versatility and reliability with a broad range of potential applications in medicine and basic human brain science. We consider here, more theoretical implications of brain tissue volumes. Specifically, we suggest that volume is an evolutionarily and developmentally regulated fundamental property of tissue, in this instance the brain and its component structures. Within this framework (1), regularities in relative variation of volumes with respect to mean volume of a structure are viewed as systematic manifestations of the rules of histogenetic process (2), regularities in the relative strength of correlation of volumes of structures are suggested to reflect constraints which serve systematically the requirements of neural systems operation. These hypotheses, if supported by extensive observation, may guide the design of applications of MRI based volumetric analysis of the human brain. © 1999 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

The newly emerging science of MRI-based brain volumetrics is concerned with the organization and analysis of qualitative and quantitative relationships between volumes and shapes of the structural components of the human brain. MRI-based brain volumetrics is already established as a methodology of great versatility and reliability with a burgeoning range of potential application in the medical biology of the human brain. As a methodology it has already served diverse study objectives. For example, the course of volumetric change for the entire brain and sets of brain structures has been charted for much of the human life cycle within the framework of MRI-based analysis [1–5]. Within the realm of disorders of the developing brain MRI-based volumetric analysis has contributed to the search for structural correlates of certain developmental disorders of

obscure nature, such as autism [6–11], OCD [12] and schizophrenia [13–20]. As yet another application of this methodology, MRI-based volumetric analysis has provided a criterion by which to recognize the presence of degenerative diseases and by which to characterize their rates of progression [21–25]. The thesis to be presented here, is that the conceptual framework of brain volumetrics, though rooted in the methodology of volumetric measurement, is not limited to volumetric measurement as a sole analytic endpoint. The thesis, greatly larger in scope and implication, is that volumetrics may lay claim to status as a coherent domain of brain science in its own right. Whereas, the focus here is upon volumetric analysis, we recognize that entirely parallel arguments apply equally to other domains of morphometry and in particular to the analysis of shape [26–28].

## 2. MRI-based brain volumetrics as a methodology

The perspective regarding volumetric analysis of the

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human brain to be explored here has its basis in the power and flexibility of MRI-based morphometry as a methodology. These qualities stem both from the imaging and the image analysis sides of its application [29,30]. An overview of these 'sides' of imaging, even briefly presented, is a favorable place for this theoretical 'walkthrough' to begin. A set of brains may be imaged at a single developmental stage in life or the same brain may be imaged repeatedly over time in life so that its volumetric analysis is not complicated by the unknowable modulations of volume inevitable with the death process, delay between death and tissue fixation and tissue fixation and processing. Where certain exclusions are observed, e.g. cardiac pacemakers, and where sedation is not required, the method is without risk to the subject. With respect to the more purely anatomic perspective, magnetic resonance imaging presents the brain as a gray scale signal intensity range which differentiates, approximately, the gray and white matter and CSF compartments of the brain. Volumetric analyses are allowable on such data sets in that they are algebraic transformations of the imaged brain. Point resolution expected with optimum 3D image data sets, accomplished by well tuned standard 1.5 Tesla imaging systems, may approach 1–2 mm. Newer generation higher field strength instruments may substantially improve this level of resolution.

Techniques of MRI analysis, concerned with the size of structures, have ranged from manual traces for estimates of diameters or sectional areas of structures as presented in single planes [31–34] to the application of advanced computational algorithms which estimate volumes as integrated across full 3D image data sets [1,2,4,5,35]. As a general rule the most advanced computational algorithms, those pertinent to the present perspective, share certain preprocessing routines and in particular positional normalization to a common stereotactic coordinate system and, electively, correction for signal intensity drifts. These operations are antecedent to the primary analytic operation which is segmentation of the image into its gray matter, white matter and CSF compartments. It is with the approach to the segmentation operation that there is a fundamental methodological divergence into two broad camps: one where gray-white segmentation is executed essentially automatically [36] and the other where it is largely but incompletely automated [37]. With the latter approach, the non-automated operations are guided by knowledge based user interaction.

The fully automated approach is recommended by its great efficiency and the rough and ready practicality that it presupposes no knowledge of brain anatomy. Thus, such methodology delivers volumetric computations based upon its own anatomic system and does so essentially in real time. The reliable performance of such procedures requires exceptional image quality and compensates poorly for blemishes in image execution associated with patient movement or the suboptimum performance of imaging systems, complexities which tend to haunt the real world of imaging ill patients in a clinical setting. Partially automated proce-

dures which are guided by investigator interpretation of anatomic boundaries, by contrast, requires experienced judgement for location of anatomic boundaries and also have voracious appetites for investigator time. These costs of the semiautomated approach are offset by the advantage that they allow the investigator to compensate for the limitations to image quality inherent in the real world experience of imaging.

It is our view that for the present, the performance of the two methods separate in terms of their validity in so far as this can be judged 'by eye' by the skilled human brain anatomist. By this we mean that the fully automated methods are still approximate at best, when compared with an experienced anatomic eye, as a means of specifying the borders between gray and white matter. For the present, it is our view that each of the two approaches has its appropriate uses and that these uses are more or less complementary. The automated approach would be preferred where rough approximations of volume are sufficient to the purposes of analysis and where the costs inherent in the semi-automated method are insupportable. Examples would be applications in real time in support of rapid flow clinical analysis or applications in support of functional imaging or spectroscopy. In these circumstances volumetric determinations based on full automation which are approximate may be sufficient to match the morphometric precision of the methods with which the volumetric determinations are to be correlated. On the other hand, we see the semiautomated approaches as appropriately reserved to investigative objectives which require maximum specificity and sensitivity of volumetric analysis. Future improvements in the specificity of fully automated routines may be expected to increase the range of their applications and, one would hope, eventuate in automated routines whose performance in every respect equals that of the semiautomated routines. As this objective is approached, the fully automated will come to supplant the semiautomated methods.

### 3. Brain volumetrics as a science

The theoretical foundation underlying the proposition that brain volumetrics is usefully pursued as a science in its own right may be relatively simply formulated. This thesis, for which there is both theoretical and observational support, is that volume is an evolutionarily and developmentally regulated fundamental property of tissue, in this instance the brain and its component structures [38–47]. The volume of a neural structure will reflect directly the size, shape, pattern of arrangement and densities of its diverse cellular components. The volume may be viewed as optimized to a selected functional state within the framework of a hierarchy of volume determining constraints. That is, the information processing capacity of the component will relate in some regular way to its volume; the optimum information processing capacity of the component will

relate in some regular way to its volume in relation to that of other brain components with which it is linked in distributed neural systems. From the evolutionary perspective, the brain or brain component will have a characteristic volume which reflects its optimization within the framework of constraints imposed by body and organ plan [48]. From the ontogenetic perspective the brain or brain component will have an approximately uniform volume among individuals of species, reflecting the constraints of cell and molecular biological processes operating ontogenetically in that species. In the course of normal brain development, these cell biological processes are dominated powerfully by cell internal controls but in detail are also modulated significantly by cell external mechanisms.

The foregoing considerations lead to the central theses developed here which are that volumetric regularities are systematic manifestations of the rules of histogenetic process, and that volumetric regularities serve systematically the requirements of neural systems operation. These general propositions accepted, the task of volumetric analysis becomes the identification of those volumetric parameters which are sensitive to the regularities of normal histogenetic sequence and those essential to normal systems operation. Within the framework of volumetric analysis this is a non-trivial challenge, made unwieldy by the potentially infinite number of volumetric measures that might be made. We present here a system of analysis formulated to this end as a reasoned search for regularities in the volumetrics of the normal brain. We see this as an exploratory exercise, one that is encouraged by apparent success in certain but not all of its directions in volumetric studies of the normal brain. We acknowledge at the outset that greater difficulties may

be expected with extension of this notion to the brain which has developed abnormally. We will return later to a discussion of formidable theoretical and epistemological hurdles that presently frustrate the interpretation of volumetric analyses of the human brain which has not developed normally.

#### 4. Brain volumes from brain images

A reasoned approach to volumetric analysis of the human brain based upon MR images must begin with the brain as presented in these images [29]. The gray scale signal intensity range of these images distinguishes approximately the cortical and nuclear gray matter compartments from the intervening white matter compartments. In their general size and shape and in their positions relative to each other, these recognizable subdivisions are highly regular in their expression among normal brains. Nothing explicit is revealed by this view of brain structure of either underlying cytological patterns or patterns of deployment of neural systems. However, other investigations including diffusion weighted imaging, dissection of the human brain and neural systems and cytologic analyses in primates provide a low resolution linkage between the visible gray and white matter anatomy of the human brain and its invisible cytologic and systems organization anatomy [49,50].

The system of analysis which we introduce here is, because of these considerations, keyed exclusively to anatomic landmarks constant to the normal brain and readily visible in MRImages (Fig. 1). The system begins with brain segmented according to its general forebrain, brain stem and cerebellar regions [51]. It then decomposes the forebrain

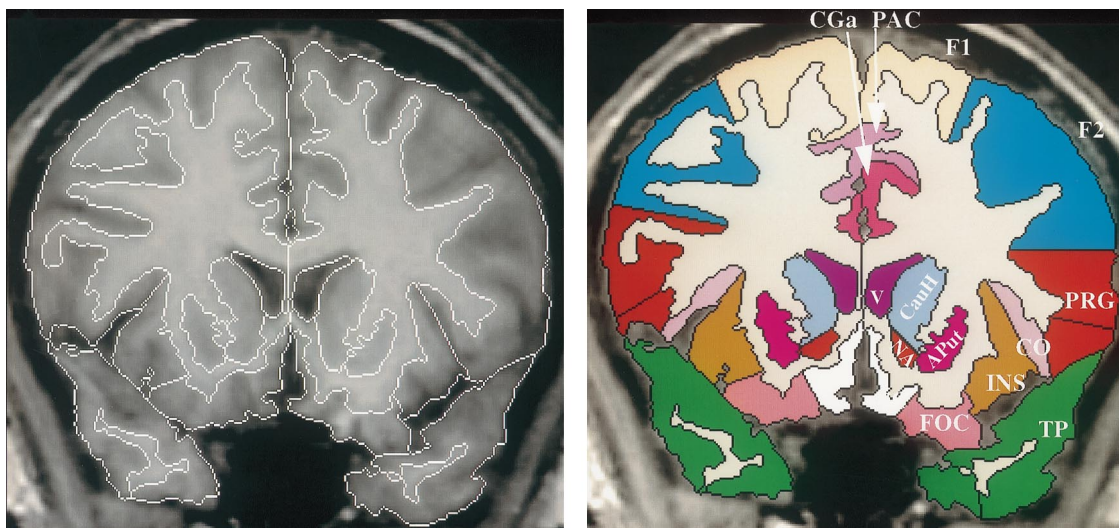


Fig. 1. The cerebrum of the human brain as viewed in the coronal plane at the level of the head of the caudate in magnetic resonance image. (A) Gray and white matter structures, distinguished visually in terms of signal intensity in T1 weighted images have been partitioned ('segmented') by contour lines constructed by semiautomated algorithm. (B) The gray and white matter structures have been parcellated by investigator interactive semiautomated algorithm. Labeled neocortical parcellation units are F1 and F2 (first and second frontal gyri), CGa (anterior cingulate gyrus), PAC (paracingulate gyrus), PRG (precentral gyrus), TP (temporal pole), INS (insula), CO (central opercular cortex) and FOC (fronto-orbital cortex). Other labels are APut (anterior putamen), CauH (head of caudate) and NA (nucleus accumbens) and V (ventricle),

into its principal cortical and nuclear structures. For greater specificity and precision of volumetric analysis these structures are, in turn, further decomposed into a very much larger set of parcels, or parcellation units [50,52–54]. The parcellation units generally respect the canonical partitions of cortex by gyri, the central gray masses by nuclei and the central white matter by its general fascicular organization. The system is relatively fine grained such that the mean volume of parcellation units is only a few percent of total volume of respective compartments. Practical or even analytic considerations could dictate a coalescence of sets of these anatomic units or indeed a further atomization. Alternate systematic treatments of forebrain anatomy or extensions of this general approach to brain stem and cerebellum are readily imaginable.

### 5. From measure of volumes to measures of regularity

The analysis yields measures of volume by region, by parcellation units or by elected combinations of these subdivisions in a single or a series of normal brains. How are these raw data to be used? More specifically, how will the analysis serve a search for volumetric regularities which analytically are specific and sensitive to more fundamental properties of brain structure? The approach we have taken is simple and straightforward in concept and execution. We derive from volumetric analysis of a set of brains:

1. The mean volumes of all structures across the hierarchy from entire brain, brain regions, segmented compartments and structures, and parcellation units.
2. Measures of variance of structure volumes about the means.
3. Measures of volume covariance of all distinct pairs of structures. The measures of mean, variance and covariance are the display of regularity in volumetric measures upon which the theoretical underpinnings of this discussion rest<sup>1</sup>. These are simply as follows.

(1) Variability of volume measures about the mean of these measures is inversely related to the strength of developmental constraints acting to determine the respective structure volume.

By illustration, the total volumes of neocortex about a mean estimate for a set of normal young adult brains, equally represented by males and females, is minimally variant. As a measure of this, the coefficient of variation (CV, being standard deviation expressed as a percentage of the mean) is only 8% (Fig. 2) [55]. By contrast the average coefficient of variation for mean volumes of neocortex for individual cerebral gyri is 25% with a substantial range of CV for individual gyri. That is, the volumetric regularities

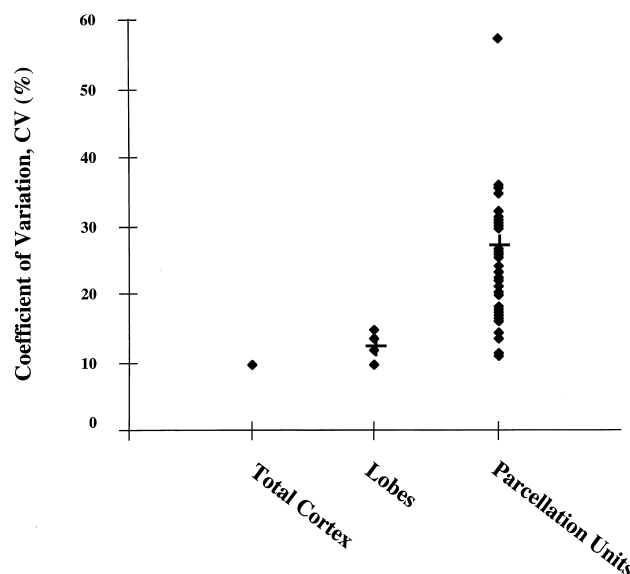


Fig. 2. Relative variation of structure volumes. Relative variation of volumes of the total neocortex, of the neocortex of the cerebral lobes (frontal, temporal, parietal, occipital) and of individual gyri are expressed as coefficients of variation (standard deviations as percentage of means). The position of the mean is indicated by a short horizontal line.

characteristic of this system are minimal variability of the volume of the overall neocortex but large variability of volumes of the individual neocortical gyri. From this we infer: (1) there are powerful ontogenetic constraints which are species characteristic acting to determine the absolute volume of the human cortex. (2) Ontogenetic constraints are greatly relaxed with respect to setting the volumes of neocortex of individual gyri. It turns out that in a series of brains of 20 normal young adults the dominant source of variance arises from individual subject  $\times$  individual gyrus interaction. This finding is consistent with other observations which illustrate the 'volume growing' effect of individual experience upon individual gyral volumes. For example the precentral gyrus (specific for motor activity) of keyboard artists is enlarged in comparison to that of subjects where the fingers are not 'overused' [56]. The degree of enlargement is systematically greater with earlier application to keyboard training across the age interval 4–6 years.

(2) Volumetric covariance of a pair of brain structures is inversely related to some measure of 'synaptic distance' or 'synaptic strength'.

By illustration, Pearson coefficients for the correlations between volumes of neocortex of precentral gyrus and putamen are substantially stronger than those between putamen and anterior lateral thalamus or anterior lateral thalamus and precentral gyrus (Fig. 3). Precentral gyrus and putamen are strongly linked at a distance of a single synapse. Linkage between putamen and anterior lateral thalamus is multisynaptic while that between anterior lateral thalamus and precentral gyrus, though a distance of only a single synapse, is highly divergent. As another illustration drawn from the observations of other investigators, the cross sectional

<sup>1</sup> We do not, however, limit our theory to these statistical summaries, sufficient if the volumetric data are Gaussian distributed. Our overall approach does not preclude examination of higher-order moments and nonlinear relationships among morphometric variables.

area of the optic tract, the volumes of lateral geniculate nucleus and striate cortex, sequential components in the primary visual relay from retina to cerebral hemisphere, have been estimated to be approximately 0.8 in a series of normal human brains studied as postmortem specimens [38]. In the cited analysis, the covariance in size of these linked structures was found not to be scaled to variation in brain size.

We postulate further that the strength of covariance for a given level of affiliation between structures (as whether ‘separated by one, two or more synapses’) will be characteristic of the system. For the present we are aware of no measures comparable to those for the visual relays [38] by which to test this hypothesis.

## 6. Complexities Inherent in Application to Developmental Disorders

We foresee a critical role for volumetric study as an approach to the biological basis of a set of developmental disorders of obscure origin and nature. We list in particular schizophrenia, autism and OCD. The conceptual and operational framework inherent in focal lesion, neurological, and behavioral deficit correlation, which has yielded much in other domains of cognitive neuroscience has illuminated only weakly our understanding of these highly prevalent and devastating conditions [57,58]. In schizophrenia and autism in particular, a preeminent disability in the domain of socialization has encouraged the view that they might be manifestations of a focally acting (or ‘modular’) process, differentially affecting the limbic lobe [7,13,18,59–64]. However, focal lesions in the limbic lobe have been neither a necessary nor sufficient structural correlate of these conditions. Greatly perplexing has been the general finding with high functioning autistic subjects but also with subjects with OCD, that the cerebrum is pervasively larger than normal with no evident consistent pattern of modular lesions or regions which are less than normal in size [9,10,12,59,65–67]. Larger brain implies either more cells or larger cells or both and one might postulate specific mechanisms of histogenetic dysregulation which could yield such an outcome. However, there is no theoretical framework, to our knowledge, from which to anticipate the information processing consequences where the volumes of regions of the brain are greater than normal.

Given that brains associated with each of these conditions may be of normal size or greater than normal size, and that for the most characteristic case, there is no evident regionally evident ‘brain lesion’, the conundrum posed by the three disorders is greatly appropriate to the volumetric analysis approach as framed here. The question to be asked in the first instance is ‘How is volume distributed?’ That is, are there structures or regions which systematically with diagnosis are deviant in their mean sizes? In fact this question has already been posed and provisionally can be answered

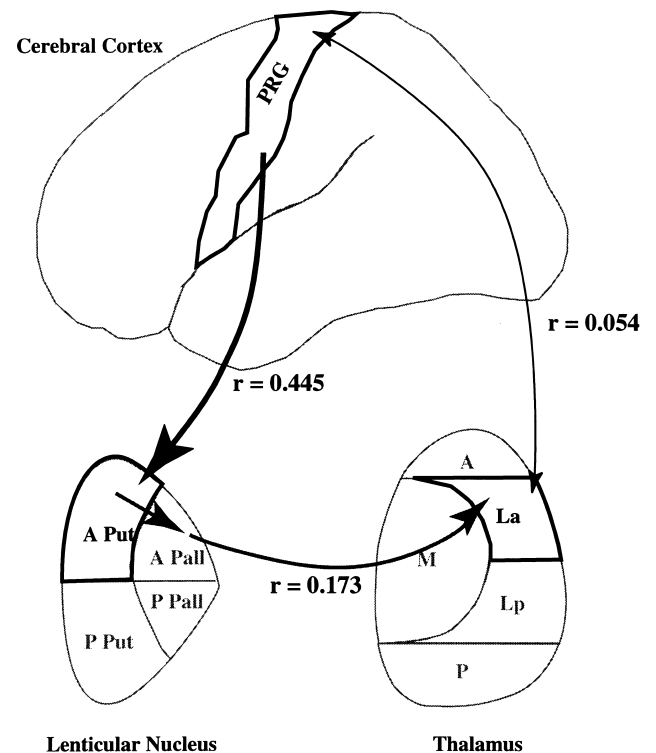


Fig. 3. Schematic representation of interrelationship between ‘synaptic distance and strength of connection’ between paired structures and the strength of correlation ( $r$  = Pearson product moment coefficients) in the variation in their volumes. This interrelationship is illustrated for neocortex of precentral gyrus (PRG) and anterior putamen (APut), anterior putamen and anterior lateral thalamus (La) and anterior lateral thalamus and precentral gyrus (1 synapse). The strongest correlation is between precentral gyrus and anterior putamen for which the synaptic distance is 1 synapse and unidirectional and the strength of interconnectivity is known to be strong. The anterior putamen and anterior lateral thalamus, separated by multiple synapses, and anterior lateral thalamus and precentral gyrus, linked weakly by reciprocal connections, are weakly if at all correlated.

with respect to analysis in dozens of cases of schizophrenia and autism which meet diagnostic criterion by state of art inquiry [20,68,69]. An as yet preliminary view of the findings is that there are some cerebral gyri which, at the 0.05 confidence level, are larger and some which are smaller than their normal counterparts. However, nothing which approaches a robust regional (or ‘modular’) pattern of volumetric abnormality has as yet been recognized.

To be determined as a next analytic step is whether the anatomic units defined in these analyses observe the codes of regularity which have emerged from analysis of the normal brain. The prediction is that they will not. Specifically the expectation is that variance will be greater about minimally variant measures such as total volume of cortex in normal brain development. Similarly the expectation is that the patterns of covariance may be entirely anomalous. Conceivably there may be no regular patterns or there may be anomalous patterns of covariance respecting strength of affiliation within systems. The sensitivity, and perhaps the specificity, of these analytic criteria to these diagnostic con-

ditions may in the end be the most important test of the utility of volumetric analysis as a program of study in human brain science.

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