Magnetic resonance-based morphometry: a window into structural plasticity of the brain

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Purpose of review

In contrast to traditional anatomical and pathological methods, magnetic resonance morphometry of the brain allows the in-vivo study of temporal changes in brain morphology and the correlation of brain morphology with brain function. Magnetic resonance morphometry has thereby recently emerged as one of the most promising fields in clinical neuroscience. This review covers the last 3 years, which have witnessed remarkable progress in this alluring new field.

Recent findings

Next to the detection of structural differences in grey and white matter in a number of brain diseases, a very important recent finding of magnetic resonance-based morphometry is the discovery of the brain's ability to alter its shape within weeks, reflecting structural adaptation to physical and mental activity. Consequently, magnetic resonance morphometry promises to be a powerful method to study disease states of the brain and to track the effects of novel therapies.

Summary

Despite these fascinating prospects, the results of morphometric studies are still dependent on the properties of the individual magnetic resonance scanner, which renders pooling of data almost impossible. It is also not known what the structural plasticity is based on at the histological or cellular level. Once these obstacles are overcome, magnetic resonance-based morphometry will become a powerful method for multicenter and therapeutic trials of several brain diseases.

Keywords

cortical thickness, diffusion tensor imaging, plasticity, structural imaging, voxel based morphometry

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Abbreviations

DBM	deformation-based morphometry
MR	magnetic resonance
VBM	voxel-based morphometry

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Introduction

Brain morphometry has emerged as one of the most dynamic fields in clinical neuroscience. With the development of novel computational techniques during the last few years and increasing image resolution, the era of magnetic resonance (MR) imaging-based morphometry has begun to expand. Recent findings and further methodological developments give hope of scientific breakthroughs that will change how we think of the brain.

Traditionally, studies of brain morphology completely depended on autopsy material. This situation changed with the advent of modern in-vivo imaging methods, in particular MR imaging. While early imaging studies of the brain provided a qualitative description of normal brain morphology and its deviations in disease states, more recently developed MR-based methods allow a quantitative evaluation of brain morphology. The whole assortment of these MR-based methods comes under the heading of MR morphometry of the brain. One of the immense advantages is the in-vivo observation of temporal changes in brain morphology and the correlation of brain morphology with brain function [1]. Normally, three-dimensional, high-resolution, T1-weighted MR images acquired with conventional 1.5 T MR scanners and 1 mm^3 voxels provide sufficient detail and contrast. Due to the extended availability of this method and consequently a great many publications in 2005 and 2006, we focus on the morphometric analysis of T1-weighted MR -imaging and will not discuss the details of white matter studies such as diffusion tensor imaging, which is covered by another paper in this issue.

Volume-based morphometry was the first technique to quantitatively assess brain structure from MR images, using regions of interest that are delineated manually or semi-manually to compute the volume of a particular structure. Thus, an inherent bias is introduced by selecting a limited number of brain regions for study. The limitations led to the development of new, automated approaches. These are all based on the idea of using a common coordinate system or atlas. Images from several subjects can be analysed together by mapping them onto a standardized coordinate space. Many laboratories have developed sophisticated algorithms and despite the large diversity, the methods can be divided into three principle categories: voxel-based morphometry (VBM), deformation-based morphometry (DBM), and surface-based

methods. This review will outline the use of these new methods for clinical applications and summarize the most important new findings.

Methods for magnetic resonance morphometry

The three novel morphometric techniques mentioned above all share the idea of applying registration algorithms to facilitate inter-subject averaging. They differ in the use of registration algorithms and parameters assessed to derive a morphometric measure.

VBM is the most commonly applied technique. It is relatively simple to use, has moderate demands on computational resources and is available in common software packages like FSL (FMRIB Analysis Group, Oxford, UK) or SPM (Wellcome Department of Imaging Neuroscience, London, UK). This technique relies on the segmentation of MR images into different tissue types (e.g. grey matter, white matter, and cerebrospinal fluid) using information derived from image intensity. The grey matter map as a result of this segmentation thus describes the spatial distribution for each individual at the level of every voxel. Additional a priori knowledge about the spatial distribution of different tissue types can be applied to refine this segmentation process. To take advantage of this approach, MR data have to be registered to the same stereotactic space as the a priori images, making the segmentation accuracy sensitive to registration errors. Because of this dependency on registration errors several approaches have been developed to improve registration accuracy, such as the use of segmented images for registration rather than MR images [2], a combined model of image registration, tissue classification, and bias correction [3•], or the application of high-resolution registration methods [4]. These solutions have been implemented in advanced VBM protocols, which then allow voxel-wise statistical testing of grey matter volume in each voxel.

Deformation-based morphometry takes a somewhat different approach. Here, the basic idea is to apply non-linear deformation algorithms to transform each subject brain to make it similar to a given template brain (normally without using segmentation). Based on the resulting deformations, the Jacobian determinant, a mathematical derivative used to restrict information on volumetric information, can be computed as an indicator of structural changes. In studies of disease progression, this technique can be used with even higher resolution, as MR imaging scans are compared intra-individually, reducing 'noise' introduced by normal variations in anatomy. Also, some recent approaches have combined processing steps of VBM and DBM [4].

Finally, the analysis of the cortical surface complements these voxel-based methods. For these approaches, the cortical surface is extracted from brain scans and further computations are applied to then calculate parameters such as cortical thickness [5] or complexity [6•]. More recently, this has also allowed the local three-dimensional computation of the gyrification index as a measure of the degree of folding of a given cortical area [7]. An advantage over VBM and DBM is the improved reduction of inter-subject variability in cortical folding patterns [8]. The extraction of the cortical surface, however, imposes high demands on computational resources and crucially depends on the quality of surface extraction, which sometimes requires additional manual correction or interaction.

The accuracy of all of the described morphometric methods largely depends on the quality of the MR images. Further methodological advances therefore rely on increasing the resolution of scans, which might succeed in resolving even layers within the cortex [9•], and also the use of advanced pulse sequences in order to additionally detect qualitative changes in the cortex, as for example subtle malformations in epilepsy that are difficult to detect on conventional MR imaging scans [10].

Imaging the normal brain

According to traditional views, the adult central nervous system is a stable, unchanging network of consolidated neuronal groups. Using morphometric techniques, subtle structural signatures regarding handedness [11], intelligence [12], age [13,14] and sex [15] have been described. A recent study [16••] investigated whether related cortical regions co-vary in grey matter density, as a result of mutually trophic influences or common experience-related plasticity. The authors found that within an individual, the grey matter density of a region is a good predictor of the density of the homotopic region in the contralateral hemisphere. The coordinated variations are likely to be determined by both genetic and environmental factors and may be the basis for differences in individual behavior [16••].

Regarding dynamic changes, it was assumed that recovery from central or peripheral nervous system damage was only possible in the neonatal, and to a certain extent, preadolescent brain. MR-based morphometry added a completely new facet to our understanding of brain plasticity in that it provided *in vivo* evidence of the capacity of the human brain not only to achieve functional reorganization [17], but to also adapt structurally with an unexpected amount of plasticity. This information has had an immediate impact on therapy. This is illustrated by an early MR morphometric study [18] that resulted in effective therapy of an idiopathic headache syndrome using selective targeting of hypothalamic deep brain structures. This ability of the brain is even apparent in healthy individuals and under normal physiological conditions. In musicians [19] and taxi drivers [20], changes in grey matter dependent on training can be shown in comparison to controls. Longitudinal studies

become especially important in this line of research. Using VBM, a significant increase in grey matter became apparent during a 3-month juggling training period [21]. After training stopped, the grey matter decreased to the original volume. This observation provides evidence for the capacity of the adult human brain to undergo dynamic morphological changes, which can take place in a matter of weeks. The exact timescale of usage-dependent structural changes, whether days, months or years is, however, still debated. A better understanding of the temporal parameters may help elucidate to what extent this type of cortical plasticity contributes to fast adapting cortical processes that may be relevant to learning and the effect of treatment. A very recent study [22] demonstrated that repetitive transcranial magnetic stimulation delivered to the superior temporal cortex causes macroscopic cortical changes in grey matter in the auditory cortex as early as within 5 days of continuous intervention. These structural alterations are mirrored by changes in cortical evoked potentials attributed to the grey matter changes and demonstrate the rapid dynamics of these processes. It is still ambiguous as to when morphometric changes can first be detected and how long the changes last. Also missing is the validation of studies that analyze the functional impact of these morphometric results.

Imaging pathology

The use of VBM has allowed the detection of structural differences in grey and white matter in a number of brain diseases including headache [18,23], stuttering [24], autism [25], schizophrenia [26,27,28•,29], epilepsy [30], depression [31,32], Parkinson's disease [33,34], Alzheimer's disease [35•], semantic dementia [36], progressive brain atrophy [37,38], multiple sclerosis [39], borderline personality disorder [40], cortical dysplasia [41]; narcolepsy [42,43], cervical dystonia [41,44], amyotrophic lateral sclerosis [45,46], Huntington's disease [47], Tourette's syndrome [48•], restless-legs-syndrome [49], Down's syndrome [50], sickle cell disease [51], head injury [52] and posttraumatic stress disorder [53], with more additions every month. In most of these studies, the reported structural changes reflect the underlying pathology and may determine the clinical phenomenology. This is particularly remarkable in 'idiopathic' diseases, for which it is generally considered that the brain structure of such patients should be normal, the problem, in essence, being one of a biochemical or biophysical nature. Such in-vivo demonstrations of a change in brain structure could represent a neuroanatomical substrate for the respective disease [54] or just an epiphenomenon or even an artefact. In this respect, any data that demonstrate a population difference between patients and controls must be regarded with caution as long it is not known whether such changes are the cause or the consequence of the disease [55]. It is unquestionable that changes in the periphery, i.e. loss of afferent input due to unilateral amputation of an extremity, may change the brain structure of individuals [56]. Recent studies also suggested that abnormalities in the cerebral cortex of subjects with amblyopia [57], strabismus [58] and even amaurosis [59•] exist, possibly as a result of experience-dependent neuronal plasticity. A future advantage in reducing the signal to noise ratio is the prospective investigation of changes within individuals. The method involves matching one image to a series of other images taken at different times for one individual. Using this approach, possible task or disease related changes in grey or white matter over time will not be corrupted by normalizing it to a template, as the gross brain shape and size is generally invariant in the same individual. Longitudinal studies, taking the individuals as their own controls, are highly sensitive to subtle task related changes which cannot be found in cohort studies [21], and the fact that the individuals will serve as their own controls renders individual structural damages such as stroke or tumours liable for investigation.

The question regarding the cellular substrate underlying such morphometric variations remains, however, unanswered. This issue could be addressed by direct comparison to histological data, which can further our understanding of the mechanisms of structural reorganization and functional restoration after injury to the central and peripheral nervous system.

Genotype effects

Brain structure is influenced by individual genetic differences. A genetic continuum was detected in which brain structure was increasingly similar in subjects with increasing genetic affinity [60]. With the thought that morphometric evidence of in-vivo changes in brain structure could represent a neuroanatomical substrate for the respective disease, it is tempting to investigate genetic traits and look for inferences with phenotype. Defining a given group by genotype is also reasonable, as the phenotype of a given disease may be heterogenetic and the results, as a consequence, false negative. Indeed, recent findings suggest that the polymorphism of certain genes [26,61••,62–64] might contribute to morphological differences between unaffected individuals. Although the results gained from these studies suggest the diagnostic use of MR-based morphometry procedures for the early detection and diagnosis of diseases such as dementia and movement disorders, to date, the clinical applicability of these markers remains uncertain. In certain diseases, MR-based morphometry provided evidence of previously unknown morphological brain changes [42], even in still unaffected individuals [65•]. In other diseases, it significantly extended current knowledge of brain morphological changes derived from autopsy studies. Nevertheless, all available clinical MR morphometric studies have their limitations. One of the major drawbacks is the poor comparability of studies from different research

centres. In addition, many studies were done in small patient samples and did not analyse the temporal dynamics and the determinants of brain morphological changes. In a number of psychiatric disorders, it remains unknown whether the observed morphological changes are a consequence or a cause of the disease. Consequently, routine clinical application of MR-based morphometry is currently not feasible.

Conclusion

As a non-invasive procedure, MR morphometry is the ideal tool for the quest to find the morphological substrates of diseases, deepening our understanding of the relationship between brain structure and function, and even to monitor therapeutic interventions. The exact cause of these lesion and training-related morphological changes in the adult brain, however, is still not known. In some respects, this situation resembles that in the functional MR imaging field some years ago, when its use for our understanding of brain function was undebated, yet the long-supposed physiological correlate of the blood oxygenation level dependent (BOLD)-signal was not yet proven [66]. Potential correlates of the observed morphometric changes include a simple change in cell size, growth or atrophy of neurons or glia, as well as changes in the intra-cortical axonal architecture (synaptogenesis). As long as the causes of these changes on a histological–anatomical level remain unresolved, the clinical relevance of MR morphometric results is limited. Important contributions to the exact causes of the structural changes will come from studies that look at the time parameters of these changes and include independent factors (i.e. electrophysiology or genetics). In addition, animal studies are a crucial and indispensable step towards a greater understanding of the structural changes found with modern morphometric techniques.

Neuroanatomical structures may be affected by age and disease, but also by genetic and even environmental factors. Computerized morphometric methods are being developed that can detect early stages in the progression of neuroanatomical changes and the consequent ability to use imaging to identify structural brain changes associated with different disease states will be useful for diagnosis and treatment. At the moment, however, the comparison of MR morphometry studies done at different research centres is almost impossible due to scanner and site-specific properties. Therefore, multicentre studies are currently only feasible with significant limitations. One of the great challenges in the future is the validation of morphometric methods as well as the development of reliable means that allow the pooling of data from several scanners and centres. With the application of these methods, MR-based morphometry will become an extremely powerful tool for multicentre and therapeutic trials of several brain diseases.

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