

Chapter 2

Morphometric Analyses in Movement Disorders

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Introduction to Magnetic Resonance Imaging (MRI) Techniques

With the aim of accurately characterizing the structural brain changes associated with neurological disorders, the spectrum of MRI techniques implemented in neuroimaging research is increasingly growing. Currently, MR data is acquired in high resolution, with optimal gray/white matter contrast and potential to provide information about white matter fiber tract orientation and integrity. Recent advances include semiquantitative and quantitative structural MR imaging, offering insight into specific brain tissue properties.

T1-Weighted Imaging

Current morphometry studies rely mostly on relative changes in brain volume and cortical thickness measured on T1-weighted images, making them dependent on MR scanner hardware, which impairs standardization for wide clinical use. T1-weighted images are widely used in brain morphometry, because they provide sufficient

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contrast between gray and white matter in most cortical areas [1]. However, there is significant age-dependant contrast decrease in subcortical structures with high iron content (e.g., pallidum) that limits the reliability of automated tissue classification algorithms in these areas particularly relevant to movement disorders.

Diffusion-Weighted Imaging (DWI)

Diffusion-weighted imaging (DWI) is sensitive to Brownian motion of molecules, thus utilizing proton behavior in brain tissue water. The most wide-spread DWI-based technique—diffusion tensor imaging (DTI), describes the restricted brain tissue water diffusion properties in three ways: (1) by predominant diffusion directions, (2) by degree of anisotropy (fractional anisotropy—FA), or (3) by magnitude of diffusion (mean diffusivity—MD) [2]. Tissue loss is commonly associated with MD increases due to enlarged extracellular spaces, while FA decreases are caused by reduction in cellular boundaries hindering diffusion. FA/MD estimates in gray matter are thought to represent variable densities of myelinated axons since the water diffusion in gray matter is almost negligible.

Relaxometry-Based Multiparameter Mapping

Relaxometry comprises advances in quantitative mapping of magnetization transfer, T1- and T2*-relaxation based on well-defined biophysical models. Quantitative MRI reproducibly maps the physical properties of water that govern MR contrast. The major contrast parameters analyzed are longitudinal relaxation rate ($R1 = 1/T1$), magnetization transfer (MT) saturation, and effective transverse relaxation rate ($R2^* = 1/T2^*$), as these reflect water content, myelination, and iron concentration [3–5]. Beyond serving as surrogate parameters, they depend on microscopic tissue properties of brain tissue. The parameter maps exhibit considerable regional variability: the largest variation is usually due to differences between gray and white matter. In addition, a comparative study demonstrated advantages of using MT saturation maps for tissue classification in basal ganglia and thalamus due to superior gray/white matter contrast [5].

Computational Neuroanatomy Methods

Computational neuroanatomy comprises diverse (semi) automated volume-, surface-, and shape-based techniques developed to investigate brain structure in cross-sectional and longitudinal study designs. We provide short descriptions of the principle methods in order to help the reader with interpretation of occasional discrepancies reported in the literature.

Data Processing

Volume-Based Methods (Volumetry)

Manual and semiautomated region-of-interest (ROI) approaches dominated the field of volumetry until computational neuroanatomy offered feasible and unbiased ways for performing whole-brain analyses. Although widely accepted in the medical community, manual 2- or 3D ROI measurements are labor intensive, subject to interrater variability, and potentially insensitive to concomitant changes in other brain regions.

Voxel-based morphometry (VBM) in the framework of Statistical Parametric Mapping (SPM, <http://www.fil.ion.ucl.ac.uk/spm>) represents a fully automated approach for volume assessment within/between cohort(s). The name is derived from the smallest spatial unit in the MR data—voxel, introduced in order to represent the 3D extent of a 2D pixel. VBM includes an iterative algorithm combining voxel-by-voxel classification (i.e., segmentation) of MR data into different tissue classes—gray matter, white matter, cerebrospinal fluid, and nonbrain voxels (e.g., skull) with registration to a common anatomical space (i.e., “spatial normalisation”). A criterion for segmentation is the intensity of a particular tissue type constrained anatomically by a priori existing tissue-specific probability maps. Subsequently, tissue-specific segments are corrected (i.e., “modulated”) for the linear and nonlinear effects of the spatial registration by using the Jacobian determinants in order to preserve the initial volumes. Following this step, the segments are low-pass filtered by convolution with an isotropic Gaussian kernel (i.e., smoothing) [6].

Surface-Based Methods

Following a segmentation step with computation of tissue class surfaces similar to the VBM, white matter surfaces can be expanded out to the gray matter/cerebrospinal fluid boundary using surface deformation algorithms. This procedure permits close matching of gray matter and white matter boundaries, such that cortical thickness can be calculated on the basis of the distance between surfaces. Image registration can be performed either in a canonical manner or using “inflated” spherical representations of the brain and surface-based coordinate systems. Subsequently, cortical thickness data are subject to spatial smoothing for statistical analysis [7].

Statistical Analyses

Imaging data is usually analyzed in the framework of Random Field Theory following the General Linear Model. The most frequently used mass-univariate models, based on least-square fitting of a General Linear Model at each voxel provide a generic

framework in which signal at each voxel is explained by a linear combination of a priori defined variables. The advantage of using mass-univariate methods is that they make spatially localized inferences that explain the disease or the clinical correlates of the particular disorder. Depending on the data representation (i.e., voxel-based or surface-based), the algorithms compute voxel- or vertex-based statistical parametric maps, which identify brain regions containing significant differences of gray matter volume or cortical thickness. Depending on the hypothesis and the questions to be addressed, one can use *t*-tests, one-, two-way independent analysis of variance (ANOVA), or multiple regression analysis. The statistical designs include a global variable (e.g., the total intracranial volume) as a covariate in order to control for global differences and focus on the regional differences in the gray or the white matter.

Recent developments in multivariate analysis of brain images allow for the classification of individual anatomical data based on prelearned characteristic patterns using support-vector machines (SVMs) [8].

SVMs are based on principles in the context of machine learning theory, where individual MR images are treated as points located in a high-dimensional space. SVM requires a measure of similarity between each pair of images. In principle, images of subjects within the same diagnostic group should be more similar to each other, than they would be to images of subjects from another group. Linear SVMs work by finding the optimal separating hyperplane that maximizes the margin between the groups. After training a SVM, there will be a number of points in the training data, which touch the hyperplanes defining the margin. The optimal separating hyperplane can be described as a simple function of these points (known as “support-vectors”). During training, the SVM assigns a specific weight to every scan reflecting the importance of that scan for group separation. Our group has further developed existing methods and applied supervised classification on data from patients with neurodegenerative diseases and healthy subjects [9].

The optimal implementation of classification methods relies on a careful study population selection, and on the minimization of variables of no interest both in patients’ and control groups. Other methods are based on the Gaussian mixture model and principal component analysis (GMM/PCA). The GMM/PCA approach extracts subject groupings from the data. Therefore, this approach does not depend on a priori knowledge of subgroups, but uses a probabilistic classification method to find the probability that a particular subject belongs to one or another subgroup. Patterns are assumed to be similar within a subgroup, but vary between subgroups [10, 11].

Application of Morphometric Analyses to Movement Disorders

The clinical routine in movement disorders often requires visual inspection of MR images by a neuroradiology specialist. The differential diagnosis of primary versus secondary forms of disease or MR signal abnormalities due to metabolite

deposition are among the most frequent referral reasons, to name a few. Computational neuroanatomy offers an unbiased way for assessment of brain structure and tissue property; however, the current status of data processing and statistical analysis limits its feasibility as a tool for diagnostic work-up.

Idiopathic Parkinson Disease (iPD)

A diagnosis of idiopathic Parkinson disease (iPD) is primarily made based on clinical criteria. Structural MRI is mainly required for differentiation from secondary forms. Nevertheless, research in the field of computational anatomy aimed to shed light on basic pathophysiology mechanisms of iPD in order to allow for early diagnosis by investigation of the relationship between brain structure and clinical signs.

Despite controversial results regarding the pattern of changes, early volumetric studies in iPD found increased age-dependant atrophy in patients when compared with controls [12–14]. Current computational anatomy research focuses on three main areas: (1) the development of MR sequences allowing for optimal delineation of the borders of substantia nigra (SN); (2) the investigation of the differential pattern of brain structure changes associated with either motor or nonmotor symptoms in iPD; and (3) the validation of computational anatomy as noninvasive diagnostic tool and predictive biomarker in early stages of disease [15].

Substantia Nigra Delineation and Connectivity

Considering the fact that loss of dopaminergic neurons is a hallmark of iPD, a considerable effort has been devoted to develop MR protocols allowing for optimal delineation and subsequent volumetric estimation of the SN. Volumetric ROI analysis based on quantitative T1 images and manual segmentation revealed significantly smaller SN volumes and a relative contrast reduction in iPD compared with controls [16]. The iron deposition in SN with increase in T2 signal motivates the usage of this technique for SN assessment resulting in particularly good correspondence to histology when applying T2*-imaging protocols [17–21]. Some encouraging results have also been obtained with fast spin-echo T1 sequences [22, 23], including measurements based on MT effects [16], which take advantage of the higher contrast offered by neuromelanin for segmenting SN from the surrounding tissue.

Recent studies investigating anatomical connectivity features of SN have demonstrated a lower connectivity probability between SN and putamen/thalamus in iPD using diffusion-based tractography. Even if not reaching statistical significance, the authors report FA reductions in the SN of iPD patients, corroborating previous findings [24]. Combining R2* and FA in the whole SN has thus far yielded the best results [25]. Unfortunately, these methods rely on a manual segmentation of the SN, which is by definition time consuming and operator dependent.

Differential Patterns of Brain Structure Changes

From a theoretical point of view, iPD patients should share a common pattern of neurodegeneration. Conversely, the existence of differential patterns of brain changes in the presence of common underlying pathophysiological mechanisms would point to a heterogeneous nature of iPD and will substantiate attempts of a novel nosological classification in clinical subtypes.

Despite the accumulating knowledge about basic principles of basal ganglia organization, the accurate characterization of the link between brain structure changes and specific symptoms has proved to be challenging. The structure–function relationship gains on relevance, particularly when trying to understand and improve recent advances in patient’s treatment offered by deep brain stimulation (DBS). This could be exemplified by the good response of rigidity and tremor to DBS, contrasting the limited effect of stimulation on balance, gait impairment, and cognitive functions.

Morphometric studies have proved to be useful when addressing specific pathophysiological questions by providing robust results mainly depending on the appropriate selection of study populations and clinical evaluations. For example, the presence of gray matter loss in parieto-temporal association areas was demonstrated to be related to higher order discriminative sensory dysfunctions, thus providing novel and relevant insight on the origin of the movement slowing typical for Parkinson disease [26]. Along these lines, Kassubek et al. [27] showed a correlation between the amplitude of resting tremor and contralateral thalamic gray matter density leaning on a theoretical assumption that the disruption of cerebello-thalamo-cortical loops is linked to resting tremor in iPD. Similarly, frontal gray matter volume reduction is associated with freezing of gait and dysexecutive symptoms corroborating the idea of movement planning deficits in iPD [28, 29]. While the majority of VBM studies in iPD show robust results, there is some controversy, which underscores the difficulty of standardizing study populations.

Concerning correlation between brain structure changes and nonmotor signs in iPD, a recent study demonstrated association between white matter loss in the right frontal lobe and depressive symptoms in iPD patients [30]. Despite limited number of observations, VBM findings confirm similar findings in major depression [31] and AD, [32] to support the evidence for limbic system involvement in iPD. Depression and apathy are invalidating and highly prevalent symptoms in the iPD population, and are a direct part of the disease rather than of reactive origin, as proved by epidemiological studies [33].

Cognitive dysfunction develops in advanced disease stages of iPD. Disentangling the neural correlates of dementia in iPD has an impact not only for this disorder, but also for understanding normal cognition. According to a recent VBM study, there is bilateral gray matter loss in the frontal lobes extending posteriorly to the lateral, medial temporal lobes, and occipital cortex in iPD with dementia (PDD) [34]. Atrophy of hippocampus and para-hippocampal gyrus was observed in Alzheimer’s Disease (AD), but not in PDD; thus, demonstrating a different

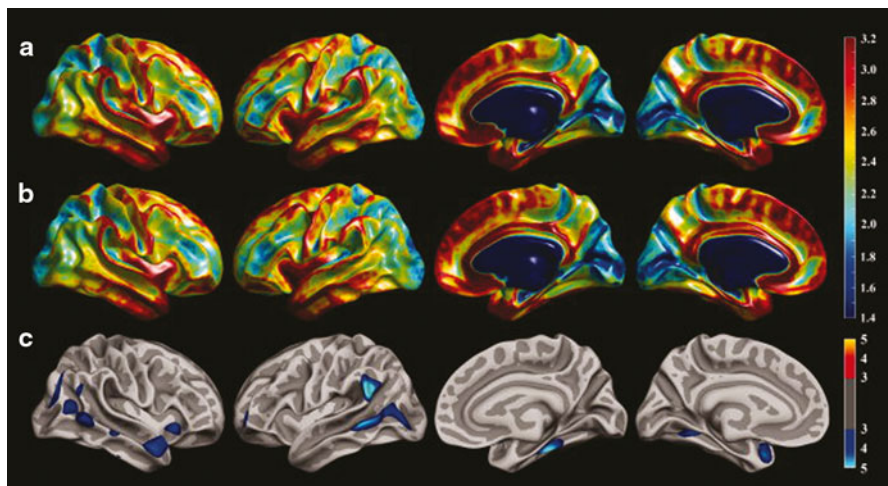


Fig. 2.1 Average cortical thickness and statistical results rendered on semiinflated white matter surface. The average regional cortical thickness of healthy controls (**a**) and patients with Parkinson's disease (PD) (**b**) are expressed as color scale. **c** The cortical areas where the thickness is thinner in patients with PD than that of controls are expressed as cold colors. The *upper* color scale bar shows cortical thickness (mm) and the *lower* color scale bar shows logarithmic scale of *P*-values ($-\log_{10}P$) [43]

pattern of neurodegeneration between the two syndromes. The presence of hippocampal involvement in PDD is still a matter of debate, and even most recent studies show controversial results [35, 36]. Studies making use of global brain structure metrics—the semiautomated assessment of white matter hyperintensities and total brain volume failed to show their significance as predictor of cognitive dysfunction in a large cohort of iPD [37, 38]. Looking for regional changes, VBM findings revealed increased regional volume loss in iPD patients with early dementia compared with those developing late dementia. The presented results are also interesting from a methodological point of view due to the fact that findings with and without adjustment for the interpolation effects of spatial normalization (“modulated” versus “unmodulated”) in the same cohorts showed no correlation, thus confirming the need to interpret “unmodulated” results as by-products of registration errors [39].

Beyond this, whole-brain VBM and ROI studies have demonstrated right fusiform and superior temporal gyrus white matter involvement as well as limbic and striatal atrophy correlating with cognitive abilities in demented and nondemented iPD patients [40–42]. The cortical thickness analysis in nondemented iPD patients revealed a widespread pattern of cortical thinning following the distribution pattern of neocortical Lewy bodies (Fig. 2.1) [43]. The investigation of subcortical structures showed a reduction of caudate volume associated with a degeneration of the dorso-lateral-prefrontal-circuit [36].

Dementia with Lewy Bodies (DLB)

A promising future direction in computational anatomy is the intention to create reliable neuroimaging biomarkers for early differentiation between DLB and dementia/parkinsonism. Contrary to ROI analyses showing volumes and atrophy rates in DLB within the normal range, the whole-brain comparison between DLB and demented iPD patients revealed greater regional volume loss in temporal, parietal, and occipital lobes for DLB patients despite the similar degree of dementia [39]. Interestingly, the pattern of volume loss in DLB was different from the frontal and temporal regional atrophy present in AD patients. According to another VBM study, DLB patients had significantly reduced right-sided fronto-temporal gray matter volume compared with iPD patients [44]. DLB patients show a characteristic pattern of white matter involvement with FA reductions in posterior regions correlating with poor performance in visuo-spatial tasks [45].

The overall conclusion from comparative morphometry studies in iPD, including AD cases, confirms the notion based on clinical experience that DLB and iPD with dementia might represent subtypes of the same spectrum of disorder with distinct patterns of brain structure changes reflecting dysfunction in specific cognitive domains.

Establishing Brain Morphometry as a Noninvasive Diagnostic and Predictive Biomarker in Early Stages of Disease

Neuropathological studies confirm the notion that at the time of first clinical signs, the underlying neurodegenerative process has been progressing for at least 10 years [46]. This motivates the continuous interest to investigate iPD-specific brain atrophy patterns bearing the theoretical possibility of high diagnostic and predictive value. The development of sensitive biomarkers at a very early clinical stage or even before symptom onset could pave the way to measure the efficacy of putative disease-modifying treatments. The assumption here is that neuroimaging can capture correlates of specific neuronal loss in early iPD.

Considering the fact that olfactory impairment is one of the first clinical signs in iPD, VBM studies focused on correlation between the degree of olfactory impairment and brain structure. Early iPD patients showed a trend for positive correlation between olfaction scores and gray matter volume in the right piriform gyrus, while moderately advanced iPD patients showed a positive correlation between olfaction and right amygdala volume [47]. Along these lines, a ROI study using DTI and olfactory testing differentiated between early-stage iPD patients and controls based on reduced FA in the anterior olfactory region [48]. Whole-brain studies in early stages of iPD demonstrated FA and MD changes in the frontal lobe white matter indicating an early microstructural damage [49, 50]. Considering the early involvement of brainstem

structures in iPD, a ROI study showed significant volume reduction in the rostral medulla oblongata and the caudal pons [51].

A common limitation of previous studies aiming at preclinical diagnosis is the inclusion of patients even at the very early stages of motor dysfunction, which could pose a hurdle to start neuroprotective drug interventions.

Atypical Parkinsonisms

Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBD) are neurodegenerative diseases pathologically classified as tauopathies. The differential diagnosis is based mainly on clinical criteria and lacks the required specificity and sensitivity. Multisystem atrophy, in its two clinical manifestations, with cerebellar (MSA-C) or parkinson-like (MSA-P) phenotype paralleled by prominent autonomic failure belongs neuropathologically to the family of synucleinopathies, but shares with PSP and CBD a more rapid progression to severe disability than iPD [52]. In early stages, the clinical manifestations of atypical parkinsonisms can mimic iPD and the differential diagnosis poses a challenge even to an experienced movement disorders specialist. Hence, numerous MR studies have attempted to find subtle morphometric differences allowing for earlier and more accurate diagnosis.

Progressive Supranuclear Palsy (PSP)

Although many studies reported successful differentiation of PSP from other forms of parkinsonism in the advanced stages of disease, there is still little evidence for an added diagnostic value of computational anatomy studies in the early phase. Volumetric and VBM studies confirm neuropathological findings with a prominent involvement of mesencephalic structures [53, 54]. The extent of cortical atrophy involves the medial frontal and lateral middle frontal gyri, the insular region comprising frontal opercula, SMA, and left mediotemporal areas [55]. The reported diagnostic accuracy distinguishing between iPD and PSP shows 84.3 % sensitivity and 79 % specificity using clinical criteria as a gold standard [56].

Corticobasal Degeneration (CBD)

Considering the substantial divergence between diagnosis based on clinical and neuropathology criteria, the existence of CBD as a clinico-pathological entity is still debated [57]. In clinically defined CBD cases, visual inspection of clinical scans can be enough to observe the typical asymmetric atrophy involving the frontal and parietal lobes. Accordingly, VBM studies in CBD showed a specific pattern of gray

matter volume reduction involving the bilateral premotor cortex, superior parietal lobules, and striatum [58]. Another piece of evidence supporting the notion about differential physiopathology of cognitive decline in atypical parkinsonism is brought by a combined pathology-VBM study showing that subcortical white matter volume reductions in PSP are the strongest predictor of cognitive impairment opposed to cortical gray matter changes in CBD [59]. Using an ROI approach, Rizzo et al. [60] computed apparent diffusion coefficient (ADC) maps from DWI data to differentiate between iPD, CBD, and PSP (Richardson syndrome phenotype). ADC changes in putamen differentiated between typical and atypical PD forms, but failed to distinguish between CBD and PSP. Interestingly, the calculated hemispheric symmetry ratio demonstrated 100 % sensitivity and specificity for accurate differentiation of CBD from PSP and iPD patients.

Multisystem Atrophy (MSA)

A number of brain structure changes in MSA—most notably putaminal atrophy—have been reported in the literature. Novel in the field of automated morphometry is the combination of VBM and voxel-based quantification (VBQ) analysis. This approach was employed to differentiate between MSA-C and MSA-P variants of MSA demonstrating more severe infratentorial volume loss in MSA-C with pronounced T2-relaxation reduction in cerebellum and brain stem [61]. Using VBM and a prospective design, Brenneis et al. [62] found widespread cortical and subcortical atrophy in MSA as opposed to normal findings in iPD. In addition, MSA patients showed a positive correlation between cortical volume loss and disease duration, and a negative correlation in the striatum. The author's supposition here was that early basal ganglia atrophy drives late onset cortical atrophy.

Diffusion parameters such as ADC raised hopes for deeper insight in the pathophysiology of atypical parkinsonism. In a recent study, ADC parameters in preselected ROIs differed between iPD, MSA, and PSP patients. In particular, ADC values in the pons, middle cerebellar peduncle, cerebellar white matter, and cerebellar dentate nucleus were higher in MSA than in PSP and controls; in PSP, they seemed to be higher in midbrain, globus pallidus, and caudate [63].

Most VBM studies are conducted at a group level and, although providing valuable information about the disease progression, are not suitable for studying the single-subject case. Manual scalar assessment of brain stem morphology characteristics have often been adopted with success, achieving differentiation of PSP from MSA with a sensitivity of 100 % and specificity of 90.5 % on the single-subject level, but suffer some operator-dependent limitations, or are extremely time consuming [64–66]. A recent study attempted to overcome these limitations by classifying quantitative structural whole-brain imaging data by employing a support vector machine approach [67]. This method proved to be quite promising, especially for differentiating PSP from iPD, with up to 96.8 % accuracy. In MSA versus iPD, an accuracy of 71.9 % was achieved; sensitivity, however, was low with 36.4 %. Interestingly, the



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