Imaging brain tissue properties in movement disorders

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Summary

Recent advances in computational neuroanatomy provide useful tools for in-vivo assessment of brain structure in movement disorders, allowing for accurate classification in early clinical stages as well as for monitoring therapy effects and/or disease progression. Current magnetic resonance imaging (MRI) derived biomarkers are mostly limited to description of relative changes in brain volume and cortical thickness measured on T1-weighted images failing to provide further insight into the underlying neurobiological mechanisms. Considering the heterogeneity of clinical presentation and the fact that pathological iron deposition and changes in white matter microstructural properties precede macroscopic volume changes in movement disorders, novel in-vivo non-invasive quantitative multi-parameter MRI approaches are developed to capture early changes in tissue characteristics beyond the atrophy pattern.

Key words: magnetic resonance imaging; movement disorders; T1-weighted; diffusion-weighted; voxel-based quantification; voxel-based morphometry

In the past two decades magnetic resonance imaging (MRI) has become an established tool to study brain anatomy in movement disorders. Aiming at identification of biomarkers for early diagnosis and therapy monitoring, a steadily growing number of studies use a wide spectrum of MR-based computational anatomy methods to provide insight into the pathophysiology of disease.

The most widespread MR techniques used in computational anatomy are T1- and diffusion-weighted imaging. While the first has a good contrast between grey and white matter of the brain, the second provides an assessment of white matter microstructure integrity. Despite the optimal contrast in cortical areas when using T1-weighted imaging, this technique has substantial limitations in subcortical regions (e.g., pallidum) relevant for movement disorders due to their high iron content. The second modality, diffusion tensor imaging (DTI), describes the restricted brain tissue water properties in two ways: by the predominant diffusion direction or by the degree of mean diffusivity. Hereby, neurodegeneration is commonly associated with mean diffusivity increases due to enlarged extracellular spaces. Both, fractional anisotropy and mean diffusivity are thought to represent densities of myelinated axons in grey matter.

Whilst the clinical routine assessment of brain anatomy in movement disorders mostly still relies on visual inspection of MR images by a neuroradiologist, recent technical and computational advances additionally enabled the application of more sophisticated unbiased analysis methods. Current structural MRI based analysis techniques provide the possibility to calculate unbiased estimates of various measurements such as grey and white matter volume (e.g., voxel-based morphometry), cortical thickness, changes in the shape of gyri and sulci.

Using established computational analysis techniques recent studies revealed significantly reduced substantia nigra volumes in idiopathic Parkinson’s disease [1]. Using DTI-based tractography the authors additionally demonstrated a lowered connectivity between substantia nigra and putamen/thalamus. Although the same study did not find any fractional anisotropy differences in substantia nigra, other studies demonstrated 100% accuracy rates for differentiation of idiopathic Parkinson’s patients and control subjects using this method [2]. Similarly, structural brain imaging has been successfully shown to facilitate differential diagnosis between idiopathic Parkinson’s disease and dementia with Lewy bodies reporting a greater volume loss in the dementia group in temporal, parietal and occipital lobes [3].

Also atypical Parkinsonism syndromes have been subject to numerous MRI studies aiming at their differentiation from each other and the idiopathic Parkinson’s disease. Their results include successful differentiation between progressive supranuclear palsy – PSP, and multi-system atrophy – MSA, with accuracies above 90%, demonstration of more severe infratentorial volume loss in the cerebellum compared to parkinsonian variant of MSA and a more widespread cortical and subcortical atrophy in multi-system atrophy as opposed to idiopathic Parkinson’s disease [2]. Diffusion-based findings using the apparent diffusion coefficient include successful differentiation between cortico-basal degeneration – CBD, idiopathic and atypical Parkinson’s disease using hemispheric symmetry ratios [2].

Other movement disorders such as essential tremor, primary dystonia, Huntington’s disease and Gilles de la Tourette syndrome have also been extensively studied using MRI with partially controversial findings [2]. For essential

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tremor, converging data, rather indicate heterogeneity of the disorder. Voxel-based morphometry comparisons between essential tremor patients and healthy controls revealed white matter changes in midbrain, occipital lobes and right frontal regions whilst grey matter changes were restricted to cerebellum. In contrast, a refined analysis of the tremor group split by anatomical distribution (arm vs head involvement) revealed a cerebellar involvement only in the head group. Complementary evidence for a white matter contribution to the disease process also comes from diffusion-weighted MRI describing cerebellar and mesencephalic white matter changes.

Similarly, structural MRI analyses demonstrated a high sensitivity of cortical thickness measurements to motor and cognitive deficits in Huntington’s disease. Voxel-based morphometry analyses confirmed striatal involvement in the disease process additionally identifying a frontal, middle temporal, insular and cerebellar network of affected regions. Additionally, both voxel-based morphometry and diffusion-weighted measurements provided complementary evidence for white matter changes with emphasis on striatopallidal connections demonstrating their usability as an accurate biomarker for presymptomatic Huntington’s disease mutation carriers.

Finally, MRI studies focusing on children and adolescents with Gilles de la Tourette syndrome demonstrated in line with clinical and theoretical disease models an involvement of basal ganglia, limbic structures and prefrontal regions in this disease process. However, these results have been questioned by more recent studies using high-precision diffeomorphic techniques, which failed to show any significant changes in basal ganglia and the thalamus. More consistently an involvement of the sensorimotor cortex was suggested by cortical thickness and fractional anisotropy analyses.

In line with our increased knowledge about the genetic basis of primary dystonia an increased number of neuroimaging studies look for genotype/phenotype interactions related to brain structure. Diffusion-based analysis techniques demonstrated reduced white matter integrity in a cerebellar-thalamic-cortical network in manifested and non-manifested DYT1/DYT6 carriers [4]. Additionally, volumetric studies reported changes in basal ganglia and in particular in the putamen in familial adult-onset primary torsion dystonia patients and in their non-manifesting family members [2].

The markedly increased number of MRI studies investigating brain tissue properties in various types of movement disorders also emphasises another important point – the necessity to develop improved MR imaging tools/techniques allowing for a straightforward neurobiological interpretation. Despite the fact that T1-weighted imaging has been shown to be a reliable biomarker of some disease-related processes it has also provided many controversial findings regarding regional involvement in specific movement disorders. This controversy might be partially explained by application of different pre-processing and statistical analyses algorithms. However, another important restriction regarding the interpretation of findings obtained using this imaging technique is its dependence on many biological parameters. T1-weighted MR contrast has been shown to be modified by many different tissue properties with iron, water and myelin content identified as main contributors to the signal [5]. This diversity of sources modifying the T1-weighted signal strongly restricts the interpretation of the underlying pathological processes (fig. 1).

A possible solution to circumvent this problem is the application of more advanced R1 and R2* based – quantitative – imaging techniques which have been shown to be selectively sensitive for distinct tissue properties such as myelin, water and iron content [5]. Studying movement disorders using these imaging techniques would facilitate the interpretation of observed tissue property changes and therewith improve our understanding of the underlying pathological processes.

References