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IN-VIVO ASSESSMENT OF SPECIFIC MICROSTRUCTURAL FEATURES OF THE BRAIN IN ALZHEIMER'S DISEASE AND ITS PRECURSORS USING DIFFUSION MAGNETIC RESONANCE IMAGING

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This thesis addresses current challenges of diffusion Magnetic Resonance Imaging (dMRI) analysis in the context of early Alzheimer's disease (AD) diagnosis. This thesis proposes a method to close the gap between the objectivity of automatic whole-brain analysis methods and the specificity of manual approaches for region-of-interest (ROI)-based analysis. The whole-brain approach for white matter (WM) analysis called tract-based spatial statistics (TBSS) is extended to allow easy ROI definition on a template WM skeleton, thus enabling tract-specific analysis (TSA) of WM while minimizing the confounding effects of partial volume (PV) from Cerebrospinal fluid (CSF) and gray matter (GM). Outlining ROIs on a template to which all individual subjects are spatially aligned eliminates the need for outlining ROIs on every subject individually and improves the stability of experimental outcomes.

In the first part of this thesis, a retrospective study presented in this thesis on data of amnestic mild cognitive impairment (aMCI) patients shows that patients who converted 12-18 months after data acquisition had already exhibited patterns of AD pathology. Similar sensitivity cannot be achieved with conventional clinical tests. The data were analysed using the tract-specific method, which proved to be easy applicable and delivered highly interpretable results, thus conforming to important requirements for use in a clinical setting.

A major challenge is to deal with the inherently low resolution of dMRI. The voxel-size of dMRI data is multiple orders of magnitude higher than the sizes of the cellular components which make up thebrain's neural tissue. Hence, parameters derived from the established diffusion tensor imaging (DTI) method reflect the combined contributions of different cellular compartments and, additionally, often contain contributions of extra-cellular CSF. The fraction of extra-cellular CSF is often increased in AD due to atrophy, which leads to different diffusion measurements that can easily be misinterpreted as seemingly microscopic effects.

The second part of this thesis demonstrates the feasibility of applying multicompartment models of diffusion in brain tissue to dMRI data of AD, thus addressing the second challenge identified in this work. These methods disentangle the effects of tissue heterogeneity and the presence of extra-cellular CSF on the measured dMRI signal, thus obtaining compartment-specific parameters which cannot be obtained with standard DTI. Analyses using these models reveal that in many cases, increased diffusivities found in DTI studies can be ascribed to an increased presence of CSF in AD patients, and that other effects are confounded by the presence of CSF. These results improve the interpretability of dMRI analyses and may shed new light on results of DTI studies presented in literature.

In summary, the presented methods and findings improve the applicability and understanding of dMRI techniques applied to the characterization and diagnosis of AD and can be regarded as an important step towards computer-aided diagnosis of AD.