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Chapter 11

Summary

The aim of this thesis was to find potential MRI biomarkers for Huntington's disease (HD). Therefore, after an overview of the current literature on MRI biomarkers **(Chapter 2)** volumetric MRI, magnetization transfer imaging (MTI), diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) were applied in patients in different disease stages of HD.

Volumetric analysis of subcortical grey matter structures demonstrated widespread involvement of the brain in general and the basal ganglia in particular. The rate of atrophy of subcortical structures as compared to whole brain atrophy was used to determine the relative speed of volume loss. Our data demonstrated that besides the caudate nucleus and putamen, also the pallidum and accumbens nucleus demonstrate strong volume reductions in the premanifest stage of the disease. Furthermore, we observed that all structures at some point show atrophy, but when compared to whole brain atrophy, the amygdala and brainstem are relatively spared in the early stage of manifest disease. Hippocampus atrophy only exceeds the whole brain atrophy rate at later disease stages. Volumetric measures were correlated to main features of the Unified Huntington's disease Rating Scale (UHDRS), namely total motor score (TMS) and total functional capacity (TFC). Volume reductions of the accumbens nucleus, putamen and pallidum are most strongly related to the motor disturbances in manifest HD, and surprisingly, the impact of the caudate nucleus is minimal. The putamen and hippocampus are related to global functioning measured by TFC; however, TFC is only applicable in manifest stages of the disease. The putamen is for both measures the most important structure **(Chapter 3)**.

Using a technique that visualizes 3D displacements of boundaries of subcortical structures (shape analysis), we showed that many subcortical regions are not uniformly reduced in volume, but show localized volume loss. In premanifest HD small areas of displacement in putamen, pallidum, accumbens and caudate nucleus were shown. Analysis of shape in manifest HD showed widespread shape differences, most prominently in the caudal part of the accumbens nucleus, body of the caudate nucleus, putamen and dorsal part of the pallidum. These specific regions all have their specific cortical projections and therefore we can use these findings and extrapolate them to functional cortical regions and clinical symptoms **(Chapter 4).**

Assessment of structural integrity of brain regions was subsequently performed using MTI. This technique, based on the exchange of magnetization between a pool of protons bound to macromolecular structures and a pool of free water

protons, allows for quantifying structural brain changes in a sensitive way. This analysis demonstrated that in the manifest but not premanifest stages loss of structural integrity is present **(Chapter 5).** MTI performed longitudinally did not show any significant reduced structural integrity in a 2-year follow up period**,** lowering the potential of MTI as a biomarker. Despite this disappointing result, an unexpected finding was that the premanifest group who was far from disease onset, exhibited increased MTR peak height in the putamen. A novel finding which could lead to new insight in compensatory mechanisms in neurodegenerative processes in HD. However these findings should be confirmed first. **(Chapter 8)**

Diffusion Tensor Imaging can be used to visualize white matter pathways and quantify integrity of these fiber bundles. DTI showed multiple white matter pathways being affected in manifest HD, but also specifically showed that the white matter projecting on the sensorimotorcortex was affected in premanifest HD. DTI disturbances showed a relationship of motor and oculomotor measures to white matter fibre bundles of the sensorimotor cortex, prefrontal cortex, thalamus and corpus callosum. Cognitive decline was related to disturbances in the corpus callosum, sensorimotor cortex and prefrontal cortex white matter pathways **(Chapter 6).**

Magnetic Resonance Spectroscopy (MRS) provided evidence that both creatine and N-acetylaspartate (NAA) concentrations are reduced in manifest HD in caudate nucleus and putamen. NAA in the putamen was found to correlate to UHDRS and TFC (Chapter 7). Moreover longitudinal analysis of metabolite changes revealed that multiple metabolite concentrations changes occur around the time of disease onset, such as NAA, creatine, choline and myo-inositol decreases. Among these NAA seems the most promising candidate for a biomarker **(Chapter 9)**.

Final concluding remarks and future perspectives are portrayed **(Chapter 10)**. Choosing the optimal biomarker for evaluating therapeutic effects is dependent on the disease stage and therapeutic compound. To evaluate the premanifest stages of the disease volumetric MRI and DTI are most suitable. When the transition period is the desired timeframe for evaluation, also MRS can be very useful, especially if the compound in question has a direct potential influence on certain pathogenic pathways which in turn have an impact on specific metabolites. Future research should focus on combining multiple imaging techniques; "multimodal imaging". A composite MRI biomarker has the potential to distinguish between disease groups more accurately than a single biomarker and in this way improve the evaluation of therapeutic compounds.