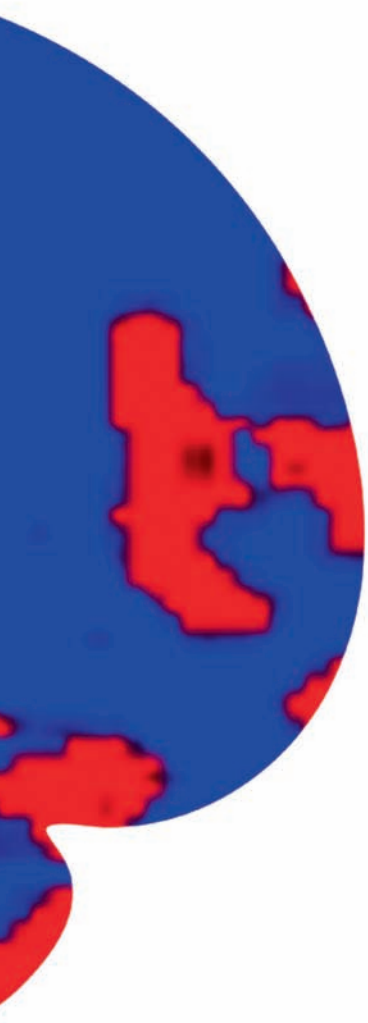
Summary



Summary

The aims of this thesis were to gain further insight into specific disease processes in HD and to identify promising biomarkers. To achieve these aims, cognitive functioning, structural brain characteristics and intrinstic functional brain connectivity of premanifest and early HD subjects were examined.

In **chapter 2**, from a review of the existing literature, we concluded that cognitive deficits show a differential progression. During late disease stages all cognitive domains show moderate or severe disturbances. The global profile of cognitive functioning in premanifest HD is characterised by subtle deficits of psychomotor speed, negative emotion recognition and executive functions. In manifest HD these deficits progressively worsen and are eventually accompanied by memory dysfunction. Global cognitive abilities and language capacities are the last to show deterioration. Eventually, these cognitive deficits in HD result in a generalised dementia.

In **chapter 3,** we demonstrated that visuospatial working memory is not only deficient in early manifest patients but also in premanifest gene carriers. Contrary to our expectations we found a 'worse-worse' phenomenon with worsened accuracy and performance speed in early HD patients. Over a period of twelve months, patients with stage two HD showed deterioration in visuospatial working memory.

In **chapter 4**, we discussed that atrophy of subcortical nuclei shows a differential deterioration profile. In premanifest gene carriers we found atrophy of the hippocampus, accumbens nucleus, globus pallidus, thalamus, brainstem, caudate nucleus and putamen. In manifest HD, further atrophy of these structures was observed, with marked loss of hippocampal volume.

In **chapter 5** magnetic resonance spectroscopy was applied demonstrating that the caudate nucleus and putamen show reduced creatine in early manifest HD suggestive of reduced energy metabolism. Furthermore, N- acetylaspartate reductions in the caudate nucleus and putamen suggests that the integrity and vitality of neurons is negatively affected in early manifest HD.

In premanifest gene carriers reduced integrity of the white matter pathway of the sensorimotor cortex, as measured with DTI, was demonstrated in **chapter 6**. In manifest HD, a more widespread pattern of reduced integrity of white matter pathways was observed.

In **chapter 7** we demonstrated that iron accumulation is present in the early stages of HD and that iron accumulation and atrophy seem to reflect independent disease processes. Increased magnetic field inhomogeneities suggestive of elevated iron accumulation were found in the putamen and caudate nucleus of early HD patients. In premanifest gene carriers elevated iron accumulation was not found in any of the subcortical structures examined.

In **chapter 8** we found evidence for reduced intrinsic functional connectivity of left middle frontal and pre-central gyrus, and right post central gyrus with the medial visual network in premanifest gene carriers. In manifest HD, a similar but more widespread pattern of reduced intrinsic functional connectivity was observed.

When all structural and functional brain changes are considered together, a broad picture of multi-level deficits begins to emerge. Cortical, subcortical and the intermediate white matter brain tissue shows evidence of structural and functional decline. We found evidence that several disease processes, such as altered metabolism, excessive iron accumulation and cell loss, play a role in the observed changes. We conclude that changes occur throughout the brain from the earliest disease phase onwards. Hence, both premanifest and manifest HD should not be regarded as a disorder of the basal ganglia, but as a disease affecting the whole brain.

Candidate biomarkers that have the potential to objectively reflect the early changes and the progressive nature of the disease are measures of subcortical atrophy, integrity of white matter pathways and of intrinsic functional brain connectivity. Iron, creatine, and N- acetylaspartate concentrations in the caudate nucleus and putamen may prove to be most useful as markers of disease state for objectifying transitional disease processes from premanifest to manifest HD. Visuospatial working memory could be applied as a state marker for stage two HD.

As clinical trials for treatment of HD become more frequent, the need for objective and sensitive biomarkers becomes more significant. Longitudinal establishment of promising biomarkers is needed. To further understanding of the complexities of HD a comprehensive approach is important for future research. Observational research of young premanifest gene carriers is important for understanding the impact huntingtin has on the developing brain. Nonetheless, observational research should always include the fullest range of gene carriers possible.