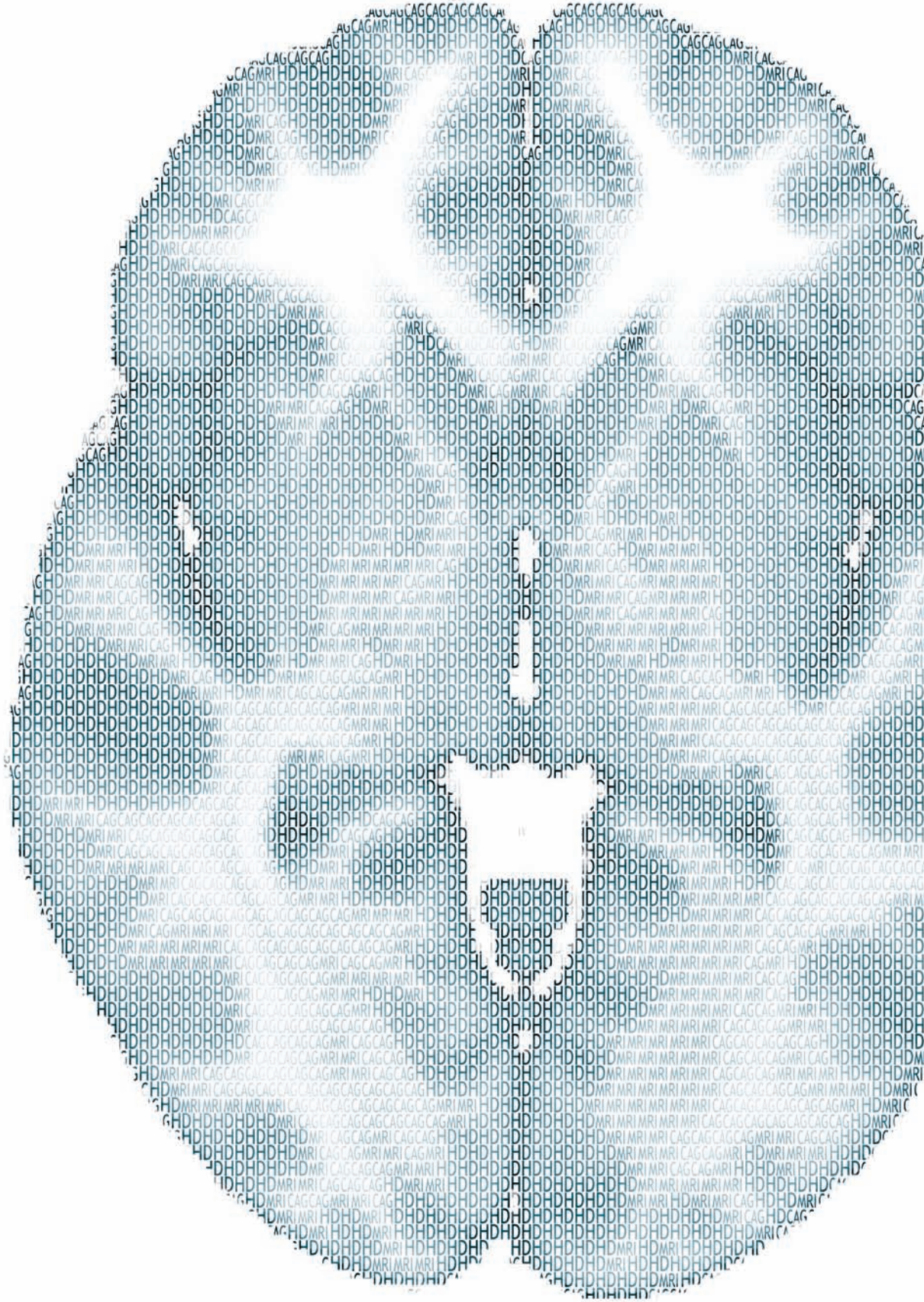

Chapter 10

Discussion, concluding remarks and future perspectives

The aim of this thesis was to find potential MRI biomarkers for Huntington's disease (HD). A hypothetical model of disease processes, MRI abnormalities and clinical signs is shown in Figure 1. These hypothetical s-shaped curves are commonly used to illustrate pathological change, whereby the pathofysiologic processes starts relatively slowly, subsequently shows a faster increase at a certain point in the pathologic cascade, and slows down towards the end. This model has been used in other neurodegenerative diseases such as Alzheimer's disease[1] and we now applied this model to HD. MRI abnormalities in HD emerge more than a decade before symptom onset[2;3]. However, the line depicting MRI abnormalities is an oversimplification in this model as many different techniques are used with different sensitivity. In this thesis volumetric MRI, magnetization transfer imaging (MTI), diffusion tensor imaging (DTI) and magnetic resonance spectroscopy (MRS) were investigated in different disease stages of HD.

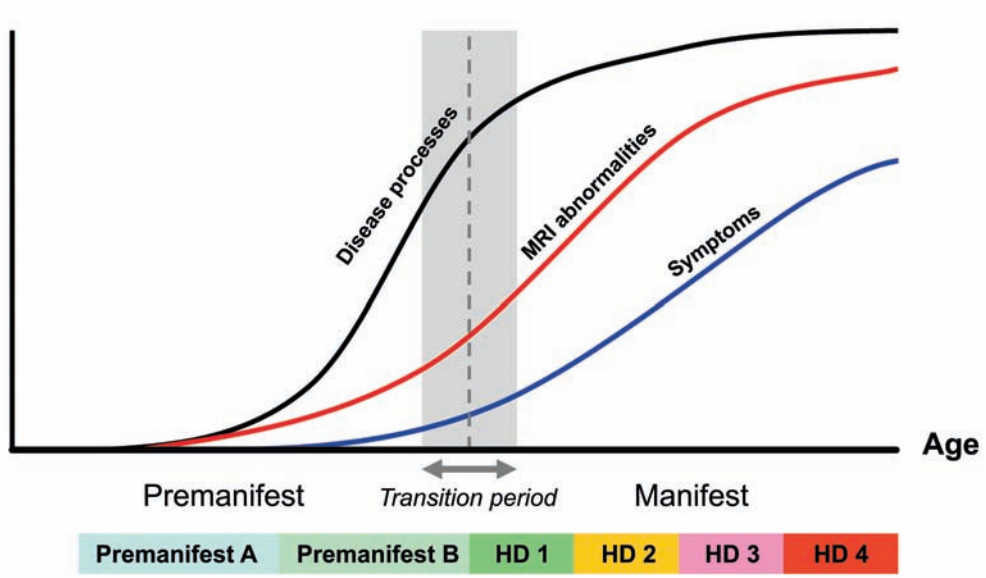

Figure 1: Hypothetical Huntington's disease model. Premanifest A = premanifest gene carriers far from expected disease onset, Premanifest B = premanifest gene carriers close to expected disease onset, HD 1 = Huntington's disease stage 1, HD 2 = Huntington's disease stage 2, HD 3 = Huntington's disease stage 3, HD 4 = Huntington's disease stage 4

MRI parameter changes per disease stage

Volumetric analysis of subcortical grey matter structures in HD have shown striatal volume decreases in premanifest and manifest stages of HD[2-4]. The volumetric

study in this thesis extended this knowledge to six other subcortical grey matter structures and demonstrated more widespread involvement of the brain and in particular the basal ganglia (Chapter 3). Furthermore, an assessment was developed regarding the rate of atrophy of subcortical structures in respect to whole brain atrophy, to determine the relative speed of volume loss. This provided insight into patterns and rate of atrophy. Besides the caudate nucleus and putamen, the pallidum and accumbens nucleus also demonstrated strong volume reductions in the premanifest stage of the disease. All structures at some point showed atrophy, however, when compared to whole brain atrophy the amygdala and brainstem were relatively spared in the early stage of manifest disease. Hippocampus atrophy only exceeded the whole brain atrophy rate at later disease stages.

To further enhance our knowledge about volume changes we applied a surface based technique, whereby localized loss of volume can be detected (Chapter 4). This technique visualizes 3D boundary displacements of specific regions in subcortical structures[5]. With this application we showed that specifically the corpus of the caudate nucleus is affected. The putamen, on the other hand, shows more uniformly distributed displacements. These regions of displacements have specific cortical projections and therefore, for striatal and all other subcortical structures, we can extrapolate these findings to functional cortical regions and clinical symptoms.

Structural integrity of brain regions was assessed using MTI (Chapter 5). This technique quantifies structural brain disturbances dissimilar to conventional volumetric MRI. When neuronal loss is present, it can be assumed that structural integrity of those regions is reduced, hence MTI parameters could potentially be a sensitive biomarker. This analysis provided the insight that in the manifest stage loss of structural integrity is present. In premanifest HD, although atrophy is present at this stage, no structural integrity loss was detected using MTI. MTI performed longitudinally did not show any significant reduced structural integrity in a 2 year follow up in either premanifest or manifest HD (Chapter 8). This greatly diminished the potential of MTI as a biomarker. Despite this disappointing result, an unexpected finding was made when the premanifest group far from disease onset exhibited increased MTR peak height in the putamen (Chapter 8). A novel finding which could lead to a new insight in compensatory mechanisms in neurodegenerative processes in HD. However confirmation of this novel finding is needed.

When neuronal degradation is present, it is not unlikely that also their axons will be affected. The structural integrity of white matter pathways is therefore of interest, providing new targets for sensitive MRI measures. DTI can be used to visualize white matter pathways and quantify integrity parameters of these fiber bundles. DTI analysis showed multiple white matter pathways being affected in manifest HD, but also specifically showed that the white matter projecting from the sensorimotor cortex was affected in premanifest HD (Chapter 6).

Tapping into more dynamic cell processes as well as structural integrity, MRS provided evidence that both energy metabolism and cellular integrity are impaired in manifest HD (Chapter 7). Moreover, longitudinal analysis of metabolite changes revealed that these changes occur in the transition phase from premanifest to manifest HD (Chapter 9).

Clinical features

The genetic defect is present from the embryonic stage[6], but when does the pathofysiological cascade of events start and lead to neuronal loss and subsequently functional loss, manifesting in clinical signs? And what period must be considered premanifest HD? In this thesis premanifest is best described as *pre-motor* manifest as the clinical inclusion criteria only describes the motor score from the UHDRS, which is a practical tool with good interrater reliability[7]. For the interpretation of all HD research, it is good to bear in mind that we label a person premanifest only by agreement about cut-off points in this clinical scale, mainly describing motor features. Cognitive or psychiatric impairments are harder to objectify. Cognition, for instance, is influenced by factors such as education. The psychiatric disturbances are difficult to link directly to HD pathology. This is especially relevant during the premanifest stage when the predictive genetic test alone causes significant stress[8].

Relating MRI disturbances to clinical measures is important but not an easy feat. It is difficult to select the appropriate participant group. If we want to encompass the whole course of HD, including the transition period, only one group, namely gene carriers (both premanifest and manifest HD), should be examined. However, the downside to this approach is that it assumes, during the total disease course, a more or less linear relationship between clinical measures of disease and MRI parameters. This is probably not the case. Performing correlations per disease stage group could help to overcome this problem. The advantage is that possible linearity problems would be less evident within these more homogeneous groups.

However the disadvantage of this approach is that the cut-off points are rigid, but the scales on which these cut off points are based can be quite variable. The second reason why relating MRI parameters to clinical measures is not straightforward is that it is hard to prove a *causal* relationship between these MRI disturbances and the observed symptoms. Conclusions based on correlations can also reflect an epiphenomenon. For example, a high UHDRS motor score can be observed in manifest HD at the same time as a reduced hippocampus volume. Correlation analysis could be significant, however hippocampal volume may not be responsible for motor score. Thus, the correlation between these two simultaneously occurring changes does not reflect causality. In this example, it is more plausible that motor disturbances occur as a result of structural changes in the motor performance networks such as volume reduction of the basal ganglia or reductions in integrity of motor cortex projections. The hippocampus is not part of the motor performance networks and its volumetric decline may result in other symptoms than motor disturbances. Thus, one should always be wary of epiphenomological results when interpreting relationships of clinical disturbances to MRI changes.

Despite the above-described difficulties in relating MRI measures to clinical measures, in recent literature the existence of a relationship seems hardly disputed. In this thesis volumetric measures were correlated to main features of the UHDRS, namely total motor score and TFC (Chapter 3). Volume reductions of the accumbens nucleus, putamen and pallidum were most strongly related to the motor disturbances in manifest HD, and surprisingly, there was no relationship of the caudate nucleus to this clinical measure. The putamen and hippocampus were related to global functioning measured by the TFC, however TFC is only applicable in the manifest stages of the disease. The putamen is the most important structure for both measures.

MTI abnormalities have a correlation to clinical measures (Chapter 5). However, there were no significant longitudinal changes in MTI parameters where clinical deterioration was evident (Chapter 8). Further assessment of structural integrity using DTI, showed a relationship with motor and oculomotor measures to integrity loss of white matter fiber bundles of the sensorimotor cortex, prefrontal cortex, thalamus and corpus callosum. Interestingly, again no relationship was found between disturbances of the fiber bundles from the caudate nucleus and clinical measures of disease. Cognitive decline was related to white matter pathway disturbances in the corpus callosum, sensorimotor cortex and prefrontal cortex white matter pathways (Chapter 6).
Using MRS a relationship of the neuronal marker NAA in the putamen was

found with UHDRS total motor score and TFC (Chapter 7). This is in line with the volumetric correlations described above. Furthermore, the caudate nucleus NAA concentration did not relate to UHDRS total motor score, again similarly to the volumetric correlations. The NAA reductions in the caudate nucleus did relate to psychiatric disturbances and TFC. Glutamate, a neurotransmitter possibly implicated in the pathofysiological pathway of excitotoxicity, showed a correlation to cognitive decline. Changes in metabolites from premanifest to manifest HD progression showed only modest correlations to changes in clinical features (Chapter 9); however, this particular analysis was performed in a predominantly premanifest HD group where clinical features are only subtle.

Considering all these correlations a pattern emerges; clinical motor measures are related to disruptions of multiple parts of motor networks, such as putamen and white matter pathways, but not to the caudate nucleus. However, the caudate nucleus is involved in global and specific cognitive functions and psychiatric disturbances. This highlights the fact that examining the individual parts of the striatum is necessary. Conversely, we should not think of any structure alone as being responsible for a single task or clinical feature. All these functions are integrated in complex networks. These correlations only tell us something about the relative contribution of each of these structures to such networks at a certain point in time.

Conclusion

Different MRI techniques have different sensitivities for detecting pathogenic changes in HD. From this thesis the temporal relationship of the examined techniques in different disease stages can be extrapolated. These temporal relationships are displayed in figure 2. Volumetric changes, especially of the caudate nucleus and putamen, show early and rapid volume reductions. Longitudinal evaluation of volumetric MRI is available from the main TRACK-HD paper[9]. DTI displays early disturbances of white matter pathways of the sensorimotor cortex. The longitudinal evaluation is not discussed in this thesis, and is thus depicted as a dotted line. However, evidence from other cross-sectional[10;11] and longitudinal[12] reports, suggestive of the high potential of DTI as a biomarker, are incorporated into this hypothetical curve. MRS parameters change close to disease onset, especially in the transition period. MTI parameters are significantly reduced in manifest HD, however the rate of change is relatively slow and is thus depicted below the clinical symptoms line. Note that the MTI line in premanifest far from expected disease onset is modestly below the x-axis, depicting the possible

increased MTR peak height of the putamen. For all techniques, this thesis only examined premanifest and early HD stages (HD 1 and 2) and thus the lines are dotted beyond this point. This hypothetical model is the interpretation of all the combined research in this thesis. It is not presented as proven fact, but rather provides a framework for future research into the MRI parameter changes in premanifest and early HD.

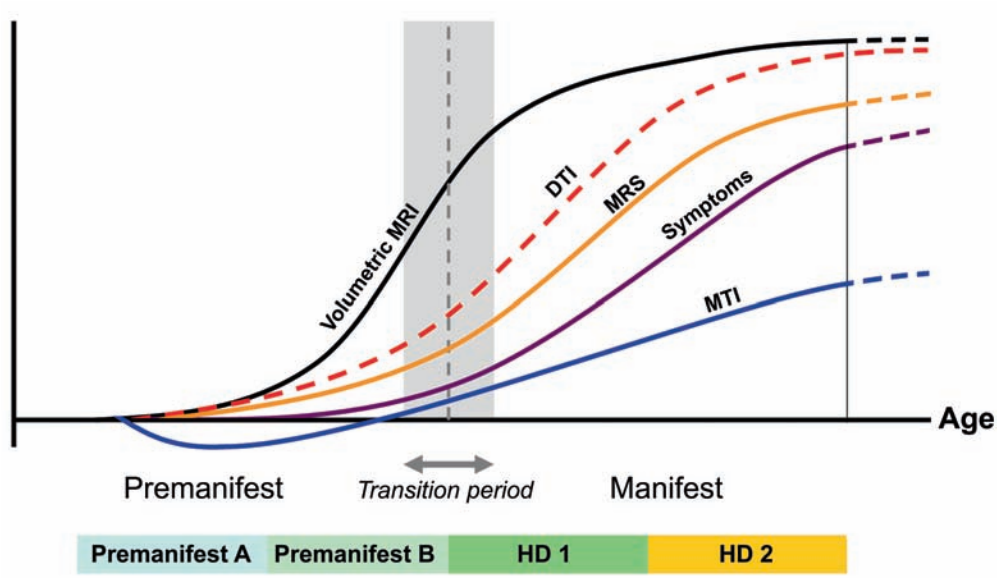

Figure 2: temporal relationships of volumetric MRI, DTI, MTI and MRS. Premanifest A = premanifest gene carriers far from expected disease onset, Premanifest B = premanifest gene carriers close to expected disease onset, HD 1 = Huntington's disease stage 1, HD 2 = Huntington's disease stage 2. DTI = diffusion tensor imaging, MRS = magnetic resonance spectroscopy, MTI = magnetization transfer imaging

Choosing the correct biomarker for evaluating therapeutic effects is dependent on the disease stage and therapeutic compound. To evaluate the premanifest stages of the disease, volumetric MRI of putamen, caudate nucleus, accumbens nucleus and pallidum and DTI of the white matter pathway of the sensorimotor cortex are most suitable. When the transition period is the desired timeframe for evaluation, MRS can also be useful, especially if the compound in question has a direct potential influence on pathogenic pathways which in turn have an impact on specific metabolites such as creatine or NAA. In early manifest HD volumetric MRI, DTI and MRS would be appropriate. With regards to volumetric biomarkers, the most appropriate structures may be different than in premanifest HD as subcortical gray matter structures show a differential atrophy pattern as the disease progresses.

Future perspectives

The future for MRI biomarkers for HD must continue in the direction of multimodal imaging. In this thesis individual MRI parameters were evaluated for their value as biomarkers. At a group level several measures were shown to be valuable; however, overlap in these measures between disease stages still exists. Thus, further improvement of the sensitivity of these MRI biomarkers is desired to accurately distinguish between disease groups. At an individual level it remains difficult to evaluate disease progression as the heterogenic clinical profile of HD is not captured by a single MRI parameter. Composite MRI-based biomarkers, based on a combination of markers with proven sensitivity for HD pathology, could be beneficial for biomarker research and have clinical applications. 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. It is not unlikely that a new compound could have an effect on one MRI parameter, but not on another. For example, when a neuroprotective agent would have a positive influence on functional MRI, but not on volumetric MRI, a possibly valuable effect of such a compound could be missed. Furthermore, it could lead to an improved understanding of the structural-functional relationship during the disease course. On an individual level it could lead to a better prediction of disease onset than genetic models currently allow. The first reports on multimodal imaging are now emerging in both HD[13;14] and Alzheimer's disease[15], showing the potential of this approach. These reports also show that a multimodal approach does not have to be limited to MRI parameters, but can also incorporate other imaging techniques such as positron emission tomography (PET).

Taking the multimodal imaging approach a step further, it is even worth considering constructing a model summing or averaging all these variables into a so-called 'HD-quotient' of MRI parameters. However the sensitivity and utility of such a quotient is highly speculative. Large longitudinal multicentre trials, such as TRACK-HD[2] and PREDICT-HD[16] are ideal platforms to apply multimodal image sequences. The challenge lies in combining all current and future data generated by these studies.

As a final remark, it must be noted that eventually a clinical endpoint is always needed to confirm a therapeutic effect. However, in the absence of appropriate clinical endpoints, the use of surrogate endpoints in the form of MRI parameters is invaluable to HD research.

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