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Functional and structural neuroimaging in Huntington's disease

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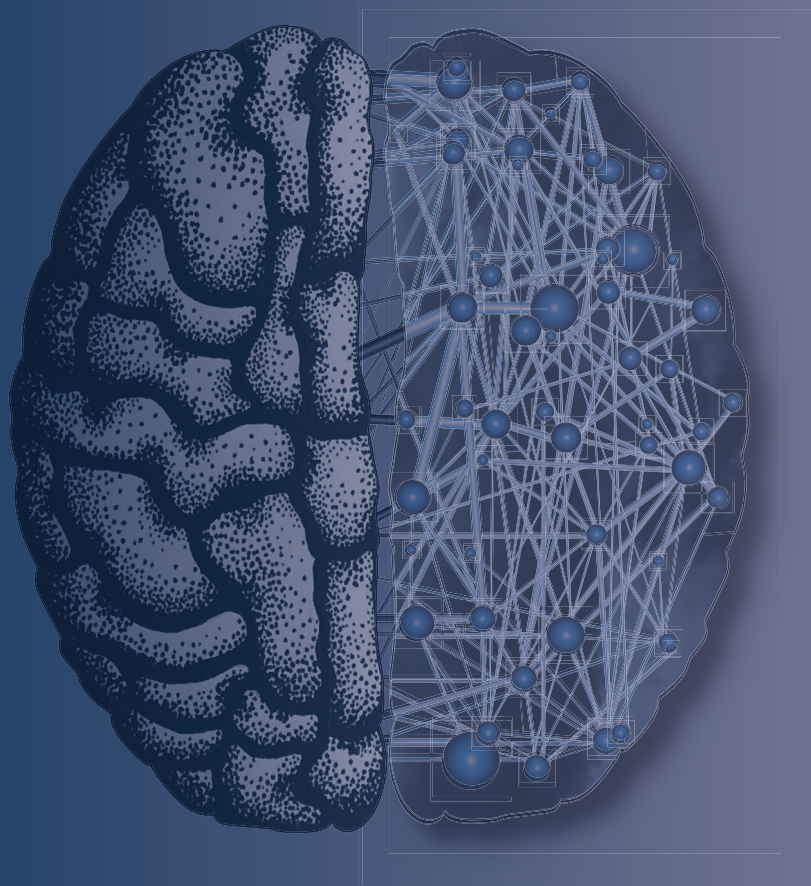


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Summarizing remarks and future perspectives

CHAPTER 8

Summarizing remarks and future perspectives

The neuroimaging and neurophysiological findings presented in this thesis add several important insights into the potential usefulness of these parameters as biomarkers in Huntington's disease (HD). A wider understanding of structural and functional brain pathology at different stages of HD also enables us to formulate recommendations for future research. Using resting state functional magnetic resonance imaging (RS-fMRI), diffusion MRI, electroencephalography (EEG) and visual evoked potentials (VEP), we have provided a broad view into the interplay of structure and function in HD neuropathology and between disease state and progression. Using these methods, we laid out potential suitable objective surrogate clinical trial endpoints and enhanced our understanding of the (subclinical) change in the disease.

We could not demonstrate any longitudinal differences in functional connectivity changes between premanifest HD (preHD) subjects and healthy controls using RS-fMRI over a period of three years (**Chapter 2**). This was unexpected, as earlier cross-sectional results suggested that functional connectivity, at the group level, was a fairly sensitive measure to differentiate preHD subjects from controls.¹ Despite the fact that we used three different analysis methods, we could not demonstrate any longitudinal change in functional connectivity within our cohort in a time frame of three years with two measurement points. At the same time, striatal atrophy rates were significantly higher in preHD compared to healthy controls. Therefore, we concluded that these results indicate an inferior sensitivity of RS-fMRI in demonstrating longitudinal changes in the preHD population compared to volumetric striatal MRI measures. We speculate that the reason for the lower sensitivity is due to the low signal-to-noise ratio of RS-fMRI compared to volumetric measures. Alternatively, this might be due to compensatory mechanisms responsible for apparently normal brain function in preHD despite ongoing neurodegeneration. Either way, the conclusion is highly relevant in light of longitudinal biomarker research in preHD, suggesting that RS-fMRI may not be a feasible marker for assessing the efficacy of an intervention in this population during a realistic clinical trial time frame.

Using diffusion tensor imaging (DTI) we showed global as well as striatal microstructural brain abnormalities at different stages of HD as well as significant associations between neurocognitive and diffusivity measures (**Chapter 3**). Performance on the Symbol Digit Modalities Test (SDMT) was mostly associated with white matter diffusivity measures, whereas performance on the Stroop Word Reading task was only associated with grey matter diffusivities. These findings may guide the selection of the most suitable cognitive measures to assess, depending on the prime target of a treatment intervention. This study did not reveal any significant longitudinal differences in microstructural organization between manifest HD, preHD and healthy controls within the two-year study period. These results were also unexpected, as neurodegeneration in HD is a slow process and microstructural alterations are expected to be present before macrostructural abnormalities become apparent. However, this method was clearly less sensitive in detecting any longitudinal changes when compared to studies using longitudinal volumetric MRI measures (particularly of the striatum). This is most likely caused by the lower signal-to-noise ratio of

this method compared to volumetric MRI methods. Alternatively, this could be due to a true absence of observable significant alterations in the diffusion profile of the examined global and striatal structures using DTI in the two-year time frame. Nonetheless, this study did provide some interesting insights into the microstructural organization of the (pre)HD brain. In manifest HD we found a diffusivity pattern which could reflect an increase in tissue permeability, extracellular space fluid, and/or interaxonal spacing due to neural tissue loss. This pattern of diffusivity changes has been associated with chronic white matter degeneration.^{2,3} In the preHD group we found that only the axial diffusivity of the white matter was significantly higher than that of healthy controls, a finding that may indicate axonal atrophy. These findings suggest that both axonal degeneration as well as myelin abnormalities play an important role in white matter pathophysiology of HD and are present throughout the entire brain. Given that the earliest detected abnormality is a higher axial diffusivity of the white matter in preHD subjects, this may point to axonal degeneration as preceding the pattern of chronic white matter degeneration found in later stages of the disease, reinforcing previous findings and further supporting this hypothesis.⁴

In a first-of-its-kind study in HD, we applied longitudinal graph theoretical analysis (GTA) to diffusion MRI (**Chapter 4**). Using this method, we described the dynamics of the connectome and characterized regional and global topological properties of brain networks in different stages of HD compared to healthy controls. By applying this method, we departed from the traditional neuroimaging approach of examining individual components of the brain, such as regions of interest, towards characterizing regional or global structure of networks. We showed both baseline and longitudinal differences between the different groups and correlations between graph metrics on the one hand, and clinical and behavioural measures on the other hand, providing us with novel insights into the dynamics of brain neuropathology occurring in HD. For instance, both the left orbitofrontal cortex and left paracentral lobule were affected longitudinally in early manifest HD as well in preHD-B (the group with the closest expected proximity to the occurrence of characteristic motor symptoms, which define the manifest stage). The orbitofrontal cortex is involved in decision making and cognitive and emotional processing, processes that are known to be progressively impacted in HD.⁵ The paracentral lobule, a component of the sensorimotor system has previously been implicated in HD where atrophy was also demonstrated.⁶ In the combined preHD group, the left medial prefrontal cortex was impacted when compared to healthy controls. This region is involved in planning and problem solving and a previous study linked reduced functional connectivity in the region to impaired executive function in HD.^{7,8} These findings provide potential clues to the structural correlates of the reductions in higher cognitive capabilities occurring in gene carriers prior to manifestation of motor signs. We also showed that the small-world organization was preserved in preHD and early HD. We suggested that intervention could be aimed at preserving this brain organization quality associated with health, especially because of the presumed degradation of this network quality in advanced stages of the disease. Such a disruption in later stages of HD is yet to be established, but is suggested by the (non-significant) decreases we have observed in our cohort. Longitudinal increases in the Unified Huntington's Disease Rating Scale total motor score (UHDRS-TMS) were negatively associated with small-worldness in the early manifest HD group, indicating that a decrease in

‘wiring-efficiency’ was related to an increase in motor symptoms. A noteworthy finding in preHD was the hub-status gain of the right superior parietal gyrus in the second visit, as this structure has been previously implicated in a compensatory role for maintaining normal motor function in preHD.^{9,10} We concluded that assessing the connectome not only provides a novel approach with a biomarker potential in HD, but also potential new insights into compensatory strategies of the brain in neurodegenerative disorders. Previous studies of the connectome in other neurodegenerative disorders such as Alzheimer’s disease had already shown the usefulness of this approach.^{11,12}

We investigated longitudinal microstructural changes occurring in the occipital cortex in different stages of HD (**Chapter 5**). This structure has not been the primary focus of HD research, even though mounting evidence has suggested early involvement of the occipital regions in HD neurodegeneration.^{13–15} We found some distinctive disease stage-specific longitudinal differences in HD as well as correlations with behavioural measures. We concluded that these findings provide added evidence of a strong involvement of the occipital cortex in HD neuropathology. Moreover, as these findings were highly significant and obtained using a fully automated method, we concluded that this approach is an objective biomarker candidate in HD. The two-year duration of the study is also feasible for evaluating the potential effect of an intervention trial. In preHD-B patients, only the middle occipital gyrus showed a significant longitudinal difference in the diffusivity profile suggesting that this structure may be the earliest involved in the neurodegeneration cascade of the occipital regions in HD. We discussed that although no specific visual symptoms are known to exist in HD, performance in visuospatial, visuomotor, as well as emotion recognition is known to be impaired.^{16–18} We suggested that investigating the occipital cortex as a region of interest may provide a more sensitive way to track disease advancement in preHD compared to the corpus callosum and/or cingulum.¹⁹ Based on our findings, we hypothesized that disruption of cell boundaries due to neural tissue loss in the occipital cortical region during disease progression causes an increase in tissue permeability and interaxonal spacing. Although the reason for a preferential neurodegeneration of the occipital region in HD remains unknown, we speculate that this might be due to the high metabolic demand of this region making it more exposed to excitotoxicity.

Turning our attention to electrophysiology, we explored quantitative electroencephalography (qEEG) measures as potential biomarkers in HD (**Chapter 6**). In this cross-sectional study we created a high-quality classifier using a machine learning algorithm. In summary, we were able to separate EEGs of HD and healthy control subjects with an accuracy of over 80%. We concluded that this automatic classification method has a potential for further development as a biomarker in HD. Interestingly, we found strong correlations between qEEG measures, the UHDRS-TMS and SDMT, both clinical markers known to be altered in a longitudinal fashion in the (pre-) manifest state. We hypothesized that the differences found in this study are primarily derived from a deregulation of brain network oscillations through GABAergic dysfunction in HD. As this was a cross-sectional study, we need longitudinal studies to evaluate the potential usefulness of this method as a biomarker in HD. We do expect this potential to be present given the findings

of strong correlations with clinical markers of decline supporting the notion of a measurable progressive change in HD brain function. Correlations between qEEG and modalities changing with the progression of the disease may lead to tools based on qEEG that can help monitor efficacy in intervention studies.

Using a multimodal approach, we identified patterns that suggest a close relationship between structural organization of the visual system and efficient functional processing (**Chapter 7**). Our findings of higher diffusivity and less efficient processing within the visual system combined with reduced VEP responsivity point to a less effective visual processing system in HD. We could not, however, demonstrate correlations with the performance on two visual tasks. The latter might suggest different processing pathways for these tasks compared to the parameters of the visual system that we assessed in this study or compensatory brain activity at play. Although these results are not expected to be suitable as practical biomarkers in HD, these do provide added insights into the impact of neurodegeneration on the visual system in HD, relevant in light of findings described in Chapter 5. As the relationship between brain structure and function is highly complex, a multimodal approach such as the one we used here is most likely the best approach in attempting to elucidate such a relationship.

Future perspectives

We have presented potential HD biomarker options in the previous chapters. When viewing our findings together with these of the literature, we anticipate that a combination of different modalities and methodologies will reveal the most sensitive and accurate biomarker. In the case of (micro-)structural brain imaging, we predict that an imaging “polymarker” consisting of different imaging techniques would provide the best disease tracking measure. Longitudinal volumetric measures of the striatum combined with diffusion measures of the occipital cortex, for instance, may provide such a measure. Using machine learning algorithms to discern the best possible combination of discriminative imaging patterns is most likely a good approach to take.²⁰ On the brain function front, we do not expect (resting state) fMRI to play an important role as an effective longitudinal biomarker in HD. We do however think that EEGs analysed with advanced methods such as machine learning, may provide a biomarker of brain function in different stages of HD and as such be potentially useful in evaluating the effect of disease modifying therapies.

As stated in the introduction, HD should be viewed as a multisystem neurodegenerative disorder of the brain, which makes a multifaceted, multivariate biomarker approach a sensible one. Such a holistic approach would provide needed insights into the cascade of the different events leading to the final common pathway of neuronal dysfunction and death. We recommend using automated methods where possible to ensure the highest degrees of objectivity and to facilitate fast and standardized interpretation of data in large multi-centre studies. When using automated techniques for MRI segmentation, visual quality control remains essential.

Beyond the biomarkers investigated in this thesis, a combination with clinical and biofluid markers will be necessary to fully assess the effects of any interventional trial. These markers will provide complementary information, both on disease state and on the specific effects of a potential therapy. This is also important as the measurable effect of a therapy on the various markers may be different. Such an approach is central in elucidating the sequence in which different markers change, which in turn may help reduce the number of participants needed to demonstrate effects of an intervention by selecting disease stage-specific sensitive makers.²¹ Also, these kinds of investigations could lead to improved predictions for the expected time to disease onset on the individual level. To conclude, the keyword we recommend for future biomarker research in HD is *combination*.

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