Structure and function of the cerebral cortex in Huntington's disease

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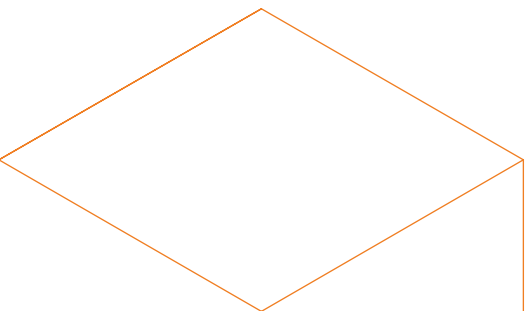
Summary, discussion and future perspectives



Although promising disease-modifying drugs are currently under investigation, there are unfortunately no effective treatment options available to date to delay or prevent the clinical onset of Huntington's disease (HD). Therefore, more knowledge about the pathophysiologic mechanisms in HD is still needed. Magnetic Resonance Imaging (MRI) is a non-invasive and objective approach to study the human brain. In the last decades, the increased use of brain imaging in HD research made it possible to better understand the natural course of the disease. MRI research in HD has been particularly focused on evaluating the onset and rate of striatal atrophy but the contribution of cortical changes remains less understood.

The aim of this thesis was therefore to investigate alterations in the cerebral cortex in HD gene carriers and assess the relationships with clinical signs of HD. Neuroimaging, neurophysiological, and cognitive measurements were used to examine structure and function of the cerebral cortex in premanifest and early manifest HD gene carriers. In this chapter, the main findings described in this thesis are summarized, discussed and recommendations for future research are provided.

SUMMARY

Brain structure

Macrostructural changes of the cerebral cortex are generally examined with volumetric MRI using different methodological techniques. Voxel-based morphometry (VBM) analysis is such a neuroimaging technique that is frequently used in brain research.[1,2] VBM involves a voxel-by-voxel comparison of the local grey matter density across the entire brain between different groups, therefore making it a sensitive approach to detect disease-specific cortical changes in regional volume.[1]

VBM analysis in our cohort of 79 early manifest HD gene carriers and 30 healthy controls showed that grey matter volume loss in HD is located in the sensorimotor cortex in the frontal and parietal lobes, and the associative visual cortices in the temporal and occipital lobes (**chapter 2**). In a smaller cohort of manifest HD gene carriers, consistent grey matter volume reductions were described in the sensorimotor and lateral occipital cortices (**chapter 3**). On the contrary, premanifest HD gene carriers only showed limited volume changes compared to controls in a small region involving the insular cortex and parietal operculum, near the sensorimotor cortex (**chapter 3**), which is consistent with previous studies.[3,4] The findings from our studies suggest that there is an decrease in cortical volume somewhere during or close after clinical disease onset, however, future longitudinal analysis is warranted to investigate this hypothesis.

Voxel-based methods measure densities per voxel separately within a brain region. Opposed to this technique, network-based analysis provides information about inter-regional changes in grey matter voxels.[5] Structural covariance networks of spatially independent grey matter regions were identified based on the co-variation of grey matter using independent component analysis (**chapter 3**). This technique is commonly used in resting-state functional MRI (fMRI) studies to assess functional connectivity.[6] When used on volumetric MRI, this technique defines spatial components based on the co-variation of grey matter patterns among an entire cohort, which can be expressed in a network integrity score.[6] Network integrity is described as the strength of an individuals' expression in an anatomical network and indirectly provides information regarding network-based grey matter alterations.

Structural covariance networks involving the precuneous, anterior cingulate, sensorimotor and parahippocampal cortices showed reductions in network integrity for both premanifest and manifest HD compared to controls (**chapter 3**). This indicates that this novel technique is sensitive to detect early grey matter changes in the cerebral cortex. The affected regions are generally involved in the planning, control, and execution of voluntary movements, visuospatial processing, and cognitive attention and control.[7,8] Domains that were all impaired in manifest HD (**chapter 3, 5, and 6**). However, since the grey matter changes were already found in premanifest HD gene carriers, our results suggest that cortical changes occur prior to clinical disease onset, in addition to striatal atrophy.[9]

Interestingly, another network comprising of the cuneus, lateral occipital cortex and lingual gyrus only showed decreased network integrity in manifest HD and not in premanifest HD (**chapter 3**), which indicates that there is an increase in cortical alterations from the premanifest phase to the manifest phase, in particular in the posterior cerebral cortex (**chapter 5**).

Subtle local volumetric differences between groups might not be detected when assessing global volumes. Measuring the thickness of the cortex with an automated method that parcellates the gyri and sulci into many small distinct regions is a frequently used method to distinguish subtle group differences.[10,11]

Rosas et al. were the first that used this technique in a small cohort of HD gene carriers to evaluate the degree of cortical thinning and reported that the earliest and most severely affected regions in HD are the primary motor, sensory, and visual cortical regions (including the superior parietal and frontal cortices).[12,13] We conducted a study in 74 HD patients in early disease stages (HD stage 1 and 2) and observed cortical thinning throughout the entire brain in HD stage 2 patients, with most severe thinning

in the parietal and occipital lobes (**chapter 4**). Our findings are therefore consistent with previous studies reporting relative sparing of the frontal and parietal brain regions early in the disease.[10,13,14] Still, in our study, HD patients in the most early clinical disease stage (HD stage 1) only showed a trend towards thinning of parietal and occipital cortices, while extensive striatal atrophy was observed in both disease stages, with up to 35% volume loss of the caudate nucleus. This implies that the rate of striatal atrophy stabilizes after clinical disease onset, whereas the degree of cortical atrophy increases. More interestingly, no associations were found between cortical thinning and striatal volume loss, suggesting that striatal and cortical degeneration might occur as two separate neurodegenerative processes (**chapter 4**).

To better understand the extent of neurodegeneration in the posterior cerebral cortex, we conducted a cross-sectional observational study with the visual cortex as region of interest. Volumetric MRI was performed to examine macrostructural alterations of the visual cortex (**chapter 6**) and diffusion tensor imaging (DTI) was used to assess the microstructure of pathways towards the visual cortex (**chapter 7**). Microstructural characteristics of fiber tracts in the brain can generally be examined based on the diffusion properties of water molecules in tissues.[15] It is proposed that changes in diffusion parameters in HD can be explained by axonal degeneration or demyelination,[16] although the specific cellular mechanism remains unclear.

Measurement of diffusion parameters along the anterior and posterior thalamic radiation tracts in manifest HD gene carriers showed signs of axonal fiber loss in the thalamus and optic radiation tract in the occipital lobe, and to a lesser degree in anterior fiber tracts in the frontal lobe (**chapter 7**). Remarkably, volumetric analysis of visual cortical regions showed reduced volumes and cortical thinning in the associative visual cortex, while the primary visual cortex did not show signs of atrophy (**chapter 6**). This latter finding is consistent with previous studies that report early involvement of associative visual brain regions, such as the fusiform gyrus, lingual gyrus, lateral occipital cortex, and cuneus in manifest HD gene carriers (**chapter 5**). Premanifest HD gene carriers, however, did not show any macro- or microstructural alterations in the posterior cerebral cortex (**chapter 6 and 7**), again suggesting that neurodegenerative changes in the posterior brain regions occur after clinical disease onset.

Brain function

The structural imaging analyses described in this thesis showed that the posterior cerebral cortex is affected in early manifest stages. Besides brain structure, we examined brain function in premanifest and manifest HD gene carriers compared to healthy controls (**chapter 6**).

In general, brain function can be measured using the different magnetic properties of oxygenated and deoxygenated blood. Activated neurons demand an increased use of energy leading to an increased blood flow in the surrounding microvasculature, which results in higher levels of oxygenated hemoglobin.[17] The change in oxygenated and deoxygenated blood levels causes alterations in MRI signal intensity, which is referred to as the Blood Oxygenation Level Dependent (BOLD) signal. Therefore, this regional hemodynamic response indirectly reflects neuronal activity in response to a task or stimulus, or at rest when measuring spontaneous fluctuations in the BOLD signal within predefined resting-state networks.[17,18] After visual stimulation using a black-and-white checkerboard stimulus, neuronal activity of the primary visual cortex was not different in premanifest and manifest HD gene carriers compared to controls (**chapter 6**). However, decreased functional connectivity at rest was present in the associative visual cortex (primarily the lingual and fusiform gyri) in manifest HD gene carriers. Our findings indicate preserved basic visual processing function and altered brain function in regions involved in higher level visual processing.
Besides the fact that we did not find structural changes of the posterior cerebral cortex in premanifest HD gene carriers, brain function also remained unaffected in this disease stage (**chapter 6**), supporting our suggestion that alterations (both structurally and functionally) in the posterior cerebral cortex only occur in the manifest disease stage.

Another approach to examine brain function is measurement of pattern-reversal visual-evoked potentials (VEP). A VEP comprises of a high contrast black-and-white checkerboard that is used as visual stimulus and the neurophysiological evoked signal is recorded with electrodes spanning the occipital region. Amplitudes (height) and latencies (length) of early components (waves) are usually considered to originate in the primary visual cortex, while late responses are thought to reflect brain activity in the associative visual cortical areas.[19]
Normal latencies were observed in premanifest and manifest HD gene carriers, indicating a preserved pre-chiasmatic function and normal conduction velocities towards and in the primary visual cortex (**chapter 7**). The reduced amplitudes that were found in HD gene carriers could suggest that axonal loss in the visual pathways due to neurodegeneration causes a reduction in signal intensity. However, we did not observe a relationship between the evoked potential measurements and clinical assessments in HD gene carriers, which might be explained by the heterogeneity in waveforms that is commonly seen due to the effects of age and gender.[20]

Clinical features

The clinical diagnosis of HD is based on the presence of motor symptoms which are measured using the total motor score of the Unified Huntington's Disease Rating Scale.[21] For this scale, motor symptoms can be divided in separate domains such as chorea, dystonia, gait disturbances, rigidity, and oculomotor dysfunction, with higher scores indicating more dysfunction.[21,22]

We related the clinical motor phenotype of 79 manifest HD gene carriers to changes in grey matter brain regions (**chapter 2**). Higher chorea scores were associated with volume loss of the striatum and pallidum, whereas higher eye movement scores were related with cortical volume loss in occipital regions. The lack of relationships between other motor symptoms, such as dystonia and gait disturbances, and changes in subcortical or cortical volumes can be explained by the fact that this cohort of early manifest HD gene carriers scored relatively low on these items. This is not unexpected, since dystonia, hypokinesia and related balance problems are often seen in more advanced stages and our cohort consisted of early stage manifest HD gene carriers.[22,23] Increased motor symptoms in HD gene carriers were also associated with reduced network integrity scores in the structural covariance network comprising of the striatum, precuneous, and anterior cingulate cortex (**chapter 3**), regions that are known to be involved in motor planning and execution.[8]

Besides motor symptoms are visual processing deficits also frequently reported in HD.[24–26] A review of the current literature showed that impairments are present in several visual cognitive domains, such as visual object perception, facial emotion recognition, visuospatial processing, and working memory, while visual hallucinations and ophthalmic disorders are rarely described in HD (**chapter 5**). Studies have unfortunately used heterogeneous cognitive test batteries to measure visual cognitive function, making direct comparisons between study findings difficult.

In our study, we used specific cognitive tasks with a large visual component that have been used previously and observed impaired visual object perception and visuospatial function in manifest HD gene carriers (**chapter 6**). However, only worse performance on visual perceptual tasks was related with reduced cortical thickness of parieto-occipital brain regions. These visual perceptual tasks required minimal motor involvement and processing speed, which implies that these tasks are a sensitive assessment of visual cognitive function.

CONCLUSIONS

This thesis provides evidence for distinct changes in cortical brain structure and brain function in early symptomatic HD disease stages. Although striatal atrophy is more extensively present in HD, changes in the cerebral cortex can also be detected in the pre-symptomatic stage. Different methodological approaches used in our studies all showed a consistent pattern of cortical atrophy making volumetric MRI a reliable and effective tool to assess early *in-vivo* cortical brain changes, even in a rare neurodegenerative disorder such as HD. Voxel-based morphometry analyses, structural covariance network analysis, and cortical thickness analyses all revealed signs of cortical atrophy in manifest HD gene carriers located in the precuneous, sensorimotor cortex, secondary and associative visual cortex, and anterior cingulate cortex. In premanifest HD gene carriers, cortical atrophy was limited to the precuneous and sensorimotor cortex. It seems that striatal volume loss stabilizes after clinical disease onset, whereas cortical atrophy becomes more pronounced. Our findings additionally imply that cortical atrophy occurs simultaneous with the onset of striatal atrophy as an independent neurodegenerative process, since the presence of cortical thinning in HD gene carriers was not related with striatal volume loss, and cortical changes were already observed in premanifest HD gene carriers close to estimated disease onset. Still, cortical changes seem to be limited to the sensorimotor areas in premanifest HD, whereas manifest HD gene carriers showed more widespread cortical alterations, with the posterior cerebral cortex as main affected brain region.

The findings of this thesis further suggest that cortical degeneration plays an important role in the presence of clinical features of HD, such as oculomotor dysfunction and visual cognitive processing deficits, while the severity of chorea, the most recognized clinical symptom in HD, is related to striatal volume loss.

We additionally examined brain function in HD using functional neuroimaging and neuro-physiological measurements, which showed that basic visual function remains preserved, even in manifest disease stages. The associative visual cortex did show changes in brain activity at rest in manifest HD gene carriers, which is consistent with our findings of impaired higher level visual cognitive functioning. The structural and functional neurodegenerative changes of the posterior cerebral cortex seems to originate in the associative visual cortices in the parietal, temporal and occipital lobes, with sparing of the primary visual cortex in the early manifest stages. Nevertheless, functional alterations of the higher-level visual cortex appear to be less pronounced and widespread than structural changes, which even extend to the inferior temporal and superior parietal cortices. Based on these findings, we can therefore conclude that structural cortical alterations contribute to the clinical signs of HD and likely precede functional brain changes in early HD.

IMPLICATIONS AND FUTURE PERSPECTIVES

Striatal atrophy is the hallmark of the disease and is linked to main clinical features of HD such as choreiform movements. Indeed, extensive volume loss was observed early in the disease, but the influence of cortical changes on other clinical signs that occur in HD should not be overlooked.

Our results demonstrate that volume loss and thinning of the cerebral cortex, especially the posterior brain regions, is detectable in early manifest stages and contributes to the presence of specific motor signs and cognitive impairments. We believe that clinical intervention trials could therefore benefit from using cortical volumes as outcome measures to assess treatment efficacy or disease progression, instead of using striatal volumes as outcome measure alone.

We described deficits in several visual cognitive domains, such as visual perceptual dysfunction and an impaired visual scanning and attention. The awareness of visual stimuli and processing of visual information is important because it is needed in daily life, for example when driving a car, during walking and in communication with others. Moreover, visual perceptual deficits might negatively impact complex cognitive task performance. While these higher-level visual processing deficits in HD are not well-recognized clinical signs of HD, it is remarkable that early involvement of the cerebral cortex seems to originate in the associative visual cortices, the regions that are generally involved in higher-level processing.

This thesis focused on the pattern of cortical changes in HD and the relation with motor and cognitive symptoms. Still, it is also important to investigate the underlying brain changes of behavioral symptoms. There are only limited studies available that assessed the neuronal correlates of behavioral changes in HD,[27,28] which is surprising since irritability, apathy, and mood disturbances are frequently reported signs in HD.[29] The presence of apathy in HD seems to be related to atrophy of the thalamus,[27] while depressive symptoms were associated with smaller volumes of the cingulate cortex.[28]

Novel disease-modifying therapeutic agents, such as huntingtin lowering drugs, are currently under development and could be promising for the treatment of HD. The study design of large multicenter longitudinal clinical trials that examine the efficacy of such drugs should therefore make use of structural and functional MRI for the assessment of both subcortical and cortical structure and function. In addition, an extensive cognitive test battery including visual cognitive tasks can be used to measure improvement of cognitive functioning. We recommend including visual cognitive tasks that are independent of other cognitive or motor processes, such as the Visual Object

and Space Perception (VOSP) tasks, in the standard cognitive battery.
Since atrophy of the posterior cerebral cortex, and in particular the visual cortex, seems to occur early in the disease, we also suggest to include volumetric assessments of the visual cortex as outcome measure in clinical intervention trials, in addition to the more standard measurements of striatal volume.

Future observational studies are continuously necessary to better understand the pathophysiologic mechanisms of the disease and the relationship with clinical signs. For a better understanding of brain function in HD, and in particular to further investigate impairments in higher-level visual processing, functional MRI using more complex visual processing tasks should be performed in future trials. In addition, it would be interesting to examine simultaneous recordings of visual-evoked potentials with functional MRI for high temporal and spatial resolution.[30,31] This way, the neural correlates of the evoked response can be better interpreted, which provides more information about functional brain changes in the posterior cerebral cortex in HD. Especially large groups of premanifest HD gene carriers (divided based on the estimated time to clinical diagnosis) should be observed over time, since this group can have considerable benefit from disease-modifying drugs.

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