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

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General introduction

Huntington's disease (HD) is a progressive autosomal dominant inherited neurodegenerative disorder, with an estimated prevalence of 5 – 10 per 100,000 in the Caucasian population.[1,2] In the Netherlands, there are approximately 1,700 individuals with genetically confirmed HD and 6,000 to 9,000 individuals that potentially have the disease but have not been tested.
In 1993, it was discovered that HD is caused by a cytosine-adenine-guanine (CAG) trinucleotide repeat expansion located on the short arm of chromosome 4p16.3 in the Huntingtin gene, which encodes the huntingtin protein.[3] Expanded repeat lengths above 36 units cause a mutation in the Huntingtin gene, which inevitably leads to clinical signs of HD, whereas in the normal population the repeat length ranges from 6 to 35 units.[2] When the disease progresses, the mutant huntingtin aggregates within different compartments of nerve cells (e.g., in the nucleus, cytoplasm and axons), resulting in cell toxicity and neuronal dysfunction.[2,4]
There is currently no effective treatment available to delay or prevent disease progression. As a result, physicians are focused on improving daily functioning by reducing symptom severity to maintain a good quality of life for the patient and their caregivers.[5]

CLINICAL FEATURES

HD is characterized by progressive motor dysfunction, cognitive decline and behavioral changes,[1,2] and is often accompanied by weight loss and sleep disturbances.[6,7] Still, the presence and severity of symptoms is very heterogeneous among individuals. Disease onset varies between the ages of 30 and 50 years with a mean disease duration of 17 to 20 years, although the disease can also occur in early childhood (juvenile HD) or later in life (late onset HD).[1,8] Longer CAG repeat lengths are associated with early clinical disease onset and more rapid progression.[1,2] Clinical disease onset is typically defined by the manifestation of characteristic motor signs, which are divided into involuntary movements such as chorea, dystonia, and tics, and impaired voluntary movements resulting in hypokinesia and apraxia.[1,9] Chorea is the most recognized sign and can be described as unwanted, irregular movements of the extremities and facial jerking.[9] The occurrence and severity of choreiform movements can vary from subtle movements of the eyebrows or upper face to more generalized contractions of the trunk and limbs.[9] Dystonia is often present in more advanced stages of the disease and is defined as intermittent muscle contractions leading to abnormal posture of the trunk and extremities.[10] Ultimately, motor symptoms will interfere with speech, swallowing, and gait stability.[1]

In general, HD gene carriers are considered to be clinically manifest based on the presence of motor signs that are related to HD, whereas premanifest HD gene carriers are defined as individuals with a confirmed expanded CAG repeat before the occurrence of substantial motor signs.[11] Still, cognitive deterioration can already be present before the onset of motor symptoms, which progresses throughout the course of the disease and eventually results in dementia.[11] Frequently reported early cognitive deficits include impairments in executive functioning (i.e., difficulties with planned behavior, attentional deficits and disinhibition), psychomotor speed, and emotion recognition.[2,11,12] The majority of HD gene carriers additionally experience behavioral changes during their lifetime.[13] Depression, irritability, aggression, obsessive-compulsive behavior, and apathy are the most frequently reported neuropsychiatric symptoms in HD.[13]

Patients become increasingly dependent in daily life, which interferes with social activities. Eventually, severe motor disturbances and behavioral changes are often the main reasons for nursing home placement.[14]

NEUROPATHOLOGY

Progressive neurodegeneration bilateral in the striatum, i.e., caudate nucleus, putamen, and nucleus accumbens, is the main neuropathological feature of HD.[15] Striatal degeneration is caused by an extensive loss of medium spiny projection neurons that form the main efferent output of the striatum towards cortical brain regions.[4,15] The presence of neuronal loss and reactive astrogliosis is, therefore, often suggested as an explanation for the clinical signs in HD.[15,16] Neuronal loss progresses along a dorsal-ventral and medial-lateral gradient, with the most early microscopic changes occurring in the body and tail of the caudate nucleus.[4,15] In addition to striatal atrophy, post-mortem studies have shown severe widespread cortical atrophy.[4,17–20] In advanced disease stages, brain weight is often reduced to 1,000 – 1,100 grams while the average normal brain weight is 1,300 to 1,500 grams.[20]

Still, it remains uncertain if cortical degeneration precedes or is secondary to striatal neuronal loss in HD and how this relates to the clinical features of HD.

BRAIN STRUCTURE AND FUNCTION

Magnetic Resonance Imaging (MRI) is a non-invasive and objective approach to quantify *in vivo* alterations in brain structure and function. In general, structural imaging modalities such as T1-weighted images and diffusion tensor imaging (DTI), measure global and regional brain volume and the microstructure of white matter fiber tracts, while functional imaging modalities assess neural activity and cell (dys-)function by detecting changes in cerebral blood flow in rest or when performing tasks.

For the diagnosis of HD, genetic testing is the gold standard. Therefore, MRI is not of diagnostic value in clinical practice. Occasionally, MRI is used to exclude other disorders in case of an atypical presentation or absent family history of HD.[21]
In HD research, MRI is primarily used as a tool to evaluate the natural progression of the disease and to find biomarkers that can be used as an outcome measure in clinical trials.[21,22] Structural imaging studies have mainly focused on changes in striatal volume and consistently observed atrophy of both caudate nucleus and putamen.[22,23] Striatal atrophy is even found a decade before predicted disease onset in premanifest HD gene carriers,[24] with a relatively linear rate of decline throughout the course of the disease.[25] As a result, striatal volume is now frequently used as a marker for disease severity, to predict time to diagnosis, or as an outcome measure in clinical intervention trials.
In addition to striatal atrophy, volumes of other subcortical and cortical brain regions are also vulnerable for degeneration early in the disease,[11,26,27] but have been studied less extensively. In clinical manifest disease stages, early cortical atrophy is thought to originate in the superior and posterior cerebral cortex, primarily in the parietal and occipital lobes, and spreads throughout the entire cortex in more advanced stages.[11,26] Atrophy of the pallidum and nucleus accumbens is found in premanifest stages of the disease,[27] but there is some controversy regarding cortical involvement in this stage. Several studies report cortical volume loss in premanifest HD gene carriers which is primarily localized in the posterior frontal, parietal and occipital brain regions,[11,28] whereas other studies report no changes, or even an increase of cortical grey matter volume in premanifest HD compared to controls.[29,30]
There is additional evidence that besides brain atrophy, the clinical manifestation of HD also results from neuronal dysfunction, tissue repair, and circuitry reorganization that can be measured using task-based or resting-state functional MRI.[31] Here, changes in the blood-oxygen-level-dependent (BOLD) signal are used to discriminate between brain regions with altered activations. In HD, functional imaging studies

showed reduced brain activity (e.g., cellular dysfunction) in heterogeneous cortical and subcortical areas after cognitive task performance (such as working memory and attentional tasks) and at rest.[31–33] Changes in functional brain networks can even be found independent of brain atrophy, implying that cellular dysfunction precedes cell death in HD.[31] However, the pattern of cortical dysfunction, the influence of structural and functional cortical degeneration on the clinical signs of HD, and associations with striatal atrophy are not yet identified.

AIMS OF THIS THESIS

The primary aim of this thesis is to examine alterations in the cerebral cortex in HD gene carriers. Different image modalities and approaches will be used to extent the knowledge on both structural and functional cortical brain changes in early disease stages and their relation to the clinical features of HD.

First, to examine the influence of brain changes on the motor phenotype in HD, we aimed to identify associations between grey matter loss and motor symptoms in early stage HD patients (**chapter 2**). To further explore the cortical coherence, we aimed to investigate alterations in grey matter brain regions using a novel technique to identify structural covariance networks in controls, premanifest and manifest HD gene carriers (**chapter 3**). In **chapter 4**, we wanted to investigate corticostriatal circuitry in HD by assessing the pattern of cortical degeneration and the relationship with striatal degeneration in early manifest disease stages.
An overview of the current literature regarding brain structure and function of the visual cortex and visual cognitive impairment in HD is presented in **chapter 5**. Here, the aim was to summarize the findings on clinical visual cognitive deficits and underlying structural and functional changes in the posterior cerebral cortex in HD.
Based on the findings reported in chapter 5, we conducted a cross-sectional study in a cohort of controls, premanifest HD gene carriers and manifest HD gene carriers. The aim was to investigate changes in structure and function of the posterior cerebral cortex in different disease stages and examine the relation with visual cognitive impairments. The findings of this study are described in **chapters 6 and 7**. Conclusions, final remarks on the findings of this thesis, and future perspectives are presented in **chapter 8**.

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