Chapter 1

Introduction and aims

In 1872 the first official publication on Huntington's disease (HD) appeared in The Medical and Surgical Reporter[1]. In his essay 'On chorea', George Huntington described a hereditary form of chorea which he noted while at work as a general practitioner in Long Island, USA. This disease became known as Huntington's Chorea, and was renamed into Huntington's disease in the eighties of the last century.

Manifest versus premanifest

Huntington's disease is a progressive neurodegenerative disease with an autosomal dominant mode of inheritance. The pathology leads to a triad of progressive clinical symptoms: motor, cognitive and psychiatric. In 1983 the genetic defect was mapped to chromosome 4, and one decade later the Huntington's Disease Research Group succeeded in generating an exact location for the HD gene[2]. With the availability of genetic testing it became possible to identify gene carriers who are still without clinical symptoms and signs, but who will inevitably progress into manifest disease. These so-called premanifest gene carriers play an important role in the understanding of the earliest damage caused by HD. Studying and mapping these early changes has become an important goal in the search for a cure for the disease.
Knowledge of the earliest conversion from healthy to disease may help to identify the fields that degenerate first, even before the appearance of overt clinical symptoms. This knowledge about the earliest pathophysiological, metabolic or functional changes could lead to the development of pharmacological agents targeting these specific fields. Currently, pharmacological research is focused on discovering disease modifying and/or disease slowing compounds, to prolong and improve the

quality of life for patients suffering from HD[3]. Identifying markers for the transition from premanifest to manifest is important for the timing of the start of therapeutic agents in individual patients. In the view of drug side-effects and health care costs it is of importance to start drug treatment at the right moment.
A key challenge in HD research is its heterogenic presentation among patients. Even when belonging to the same family, no prediction can be made about an individuals initial symptoms, age at onset, clinical presentation or disease duration. To date, no single symptom or sign has been identified as generalised marker of definite onset of disease. Most likely early changes on pathophysiological measures of the brain in combination with changes on several clinical functional measures will help to more precisely pinpoint the onset in the individual person[3].

Clinical features

HD symptoms can be separated in three domains: motor, behavioural and cognitive. The most characteristic and debilitating motor symptoms are the choreatic, or dance-like, movements. Starting as subtle twitches in arms, legs, face or trunk, and often (consciously or unconsciously) masked by other normal movements, they progress in severity throughout the whole body over several years, severely debilitating patients in their daily activities[4,5]. Other motor impairments include, amongst others, bradykinesia and dystonia[5,6]. Although the clinical diagnosis is often based on the appearance of the first overt motor abnormalities (together with a positive family history and genetic test) subtle motor abnormalities have been detected in premanifest subjects also. Here, chorea, defective oculomotor functioning, bradykinesia and dystonia have been shown to differentiate premanifest gene carriers from healthy control subjects[7,8,9].
Behavioural changes are also well recognized in HD gene carriers, sometimes more so by partners and family members than by the patients themselves. Among the most common psychiatric symptoms associated with HD are depression, apathy and aggression or irritability, resulting in progressive personality changes[10,11]. Particularly, symptoms such as depression, anxiety and obsessive-compulsive behaviour can already be seen in premanifest subjects[12].
he third main area of decline in HD is cognition. HD patients become progressively more disabled on several areas of cognitive functioning, eventually leading up to full blown dementia. HD belongs to the group of subcortical dementias, and patients often exhibit a frontal syndrome and the associated disabilities reflect the neuropathological damage to fronto-subcortical connections[13]. Typically, executive dysfunctioning (i.e. difficulties with planned behaviour, attentional impairment and disinhibition) is one of the first cognitive symptoms to appear, together with marked reductions in psychomotor and mental processing speed[14,15,16]. This is opposed to the picture of cognitive decline that we see in dementias of the cortical type, such as Alzheimers disease (AD), where severe memory loss, aphasia and

agnosia are most pronounced early on in the disease process[13]. In HD, memory deficits are also common, but less prominent than in AD[15]. Language is relatively spared until the latest stages of the disease, but will eventually also deteriorate, alongside other cognitive functions. A robust finding, which has even been found in individuals in the premanifest phase, is defective recognition of negative emotions[17]. But subtle changes in psychomotor speed, executive functioning and memory have also been detected before clinical disease onset[18 19 20]. However, variability in observed premanifest cognitive changes is large and no agreement is reached yet from the studies performed.

Nowadays, consensus is starting to form among scientists and clinicians that changes in any of the three main HD domains can already be detected in the premanifest phase, before the motor symptoms are severe enough to warrant a clinical diagnosis. The area of cognition is one of the largest research fields in HD literature, evident by the large body of articles on cognition in both manifest and premanifest HD[21]. Next to psychiatric disturbances, cognition is also one of the symptoms most debilitating for patients in daily life, even more so than the unwanted movements[6 14].

Genetics

HD is caused by an expanded and unstable trinucleotide (CAG) repeat in the huntingtin gene, leading to an expanded polyglutamine stretch in the huntingtin protein[22]. CAG repeats from 36 repeats on are associated with HD, but only repeats from 39 on are considered fully penetrant, where individuals will develop symptoms and signs of the disease within their lifetime. Repeats from 36 to 39 are regarded as a grey area, where the disease may or may not manifest[23 24]. Abnormal CAG repeat lengths have been found to be inversely related to age at onset, and they can account for up to 70% of the variability in age at onset. The remaining variability is likely influenced by both other genetic influences and environmental factors[6].
In most cases, clinical manifestation of the disease occurs in mid-life (between 30 and 50 years of age) and inevitably leads to death in approximately 15 to 30 years. To date, no cure is available for HD, and patients receive symptomatic treatment only[3 25].

Neuropathology

ven though the exact neuropathology of HD is not yet completely known, the earliest and most pronounced neuropathology is found in the striatal parts of the basal ganglia (e.g. caudate nucleus and putamen) and progresses throughout the course

of the disease[23,26]. Subsequently, neuronal loss and atrophy spread throughout the cerebral cortex, affecting both grey and white matter[27,28]. In the later stages of the disease the entire brain is affected to a greater or lesser extent, resulting in up to 25% brain weight loss in the most advanced stages[23].
Magnetic Resonance Imaging (MRI) studies have indicated that brain abnormalities in HD develop long before overt clinical symptoms and signs appear. Both structural[29,30] and functional[31,32] brain changes have been found in premanifest gene carriers up to 20 years from their estimated disease onset[33].

Motoric influence on cognitive tests

That cognitive test performance is influenced by affective disorders, such as depression, is well recognized in the literature[34], for example in Parkinsons disease (PD)[35]. Therefore, depression score is often taken into account when differences in cognitive functioning between groups are studied. However, the influence of motor disturbances on cognition has not received much attention, even though it probably has a negative impact on cognitive outcome, because almost all cognitive test require some form of motoric response (e.g. speaking, drawing, writing).
With HD primarily being a movement disorder, and together with the subtle motor changes already recognized in premanifest HD gene carriers[7], the influence of motor impairments on cognitive functioning in HD must not be neglected when doing cognitive research. However, in very few studies on cognition in HD the influence of motor impairment is accounted for.

Aims of this thesis

The main aim of this thesis was to gain more insight into the course of cognitive functioning in HD, especially in the premanifest phase. Furthermore, we aimed to minimize the influence of HD specific motor disturbances on cognitive scores, by taking the motoric influence into account making use of several different approaches.

We studied the cognitive construct of attentional control in both premanifest and manifest HD gene carriers using the Sustained Attention to Response Task (SART), a cognitive test of attention and inhibition with minimal motor demands. Moreover, the P300, an event related potential independent from motor influence, was recorded simultaneously with the SART, to more accurately measure cognitive processes free from motor influences. We investigated possible differences in attentional control and P300 characteristics between premanifest, manifest and control subjects cross-sectionally (**chapter 2**). Furthermore, we studied potential change in attentional control and P300 in our groups over a three-year follow-up

period (**chapter 3**). In **chapter 4** we studied longitudinal change in premanifest gene carriers on several cognitive tests over a seven-year follow-up period. We further investigated the natural progression of cognition by studying both manifest and premanifest subjects over a ten-year period, and compared their longitudinal change on three cognitive and one motor domain to control subjects in **chapter 5**. In **chapter 6** we explored whether differences exist in the cognitive and global profiles of two different HD motor phenotypes; predominant hypokinetic-rigid HD and choreatic HD. In **chapter 7** we present the results of a longitudinal study where we investigated the possible negative influence of motor functioning on cognition by creating an extra 'high motor low cognition' conditions for existing tests of executive functioning. We subtracted these motor conditions from the original test scores to be able to isolate more 'pure' cognitive functioning. To conclude, a general discussion and future perspectives are presented in **chapter 8**.

References

[1] Huntington G. On chorea. *the Medical and Surgical Reporter*, 26:317–321, 1872.

[2] HDCRG. A novel gene containing a trinucleotide repeat that is expanded and unstable on huntington's disease chromosomes. *The Huntington's Disease Collaborative Research Group*, 72:971–83, 1993.

[3] Sturrock A, Leavitt BR. The clinical and genetic features of huntington disease. *J Geriatr Psychiatry Neurol*, 23:243–59, 2010.

[4] Reilmann R, Bohlen S, Kirsten F et al. Assessment of involuntary choreatic movements in huntingtons disease – towards objective and quantitative measures. *Mov Disord*, 26:2267–73, 2011.

[5] Roos RA. Huntingtons disease: a clinical review. *Orphanet J Rare Dis*, 5:40, 2010.

[6] Novak MN, Tabrizi SJ. Huntingtons disease: clinical presentation and treatment. *Int Rev Neurobiol*, 98:297–323, 2011.

[7] Biglan KM, Ross CA, Langbehn DR. Motor abnormalities in premanifest persons with huntingtons disease: the predict–hd study. *Mov Disord*, 24:1763–72, 2009.

[8] Blekher TM, Yee RD, Kirkwood SC et al. Oculomotor control in asymptomatic and recently diagnosed individuals with the genetic marker for huntingtons disease. *Vision Res*, 44:2729–36, 2004.

[9] Kirkwood SC, Siemers E, Bond C et al. Confirmation of subtle motor changes among presymptomatic carriers of the huntington disease gene. *Arch Neurol*, 57:1040–44, 2000.

[10] van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified huntingtons disease gene carriers. *J Neuropsychiatry Clin Neurosci*, 19:441–48, 2007.

[11] Thompson JC, Harris J, Sollom AC et al. Longitudinal evaluation of neuropsychiatric symptoms in huntingtons disease. *J Neuropsychiatry Clin Neurosci*, 24:53–60, 2012.

[12] Duff K, Paulsen JS, Beglinger LJ et al. Psychiatric symptoms in huntingtons disease before diagnosis: the predict–hd study. *Biol Psychiatry*, 62:1341–46, 2007.

[13] Salmon DP, Filoteo JV. Neuropsychology of cortical versus subcortical dementia syndromes. *Semin Neurol*, 27:7–21, 2007.

[14] Paulsen JS. Cognitive impairment in huntingtons disease: diagnosis and treatment. *Curr Neurol Neurosci Rep*, 11:474–83, 2011.

[15] Zakzanis KK. The subcortical dementia of huntingtons disease. *J Clin Exp Neuropsychol*, 20:565–78, 1998.

[16] Duff K, Paulsen JS, Beglinger LJ et al. frontal behaviors before the diagnosis of huntingtons disease and their relationship to markers of disease progression: evidence of early lack of awareness. *J Neuropsychiatry Clin Neurosci*, 22:196–207, 2010.

[17] Novak MJ, Warren JD, Henley SM et al. Altered brain mechanisms of emotion processing in premanifest huntingtons disease. *Brain*, 135:1165–79, 2012.

[18] Papp KV, Kaplan RF, Snyder PJ. Biological markers of cognition in prodromal huntingtons disease. *Brain Cogn*, 77:280–91, 2011.

[19] Stout JC, Waever M, Solomon AC et al. Are cognitive changes progressive in prediagnostic hd? *Cogn Behav Neurol*, 20:212–18, 2007.

[20] Hart E, Middelkoop H, Jurgens C et al. Seven–year clinical follow–up of premanifest carriers of huntingtons disease. *PLoS Curr*, 3:1288, 2011.

[21] Dumas EM, van den Bogaard SJ, Middelkoop HA et al. A review of cognition in huntingtons disease. *Front Biosci*, 5:1–18, 2013.

[22] Zheng Z, Diamond MI. Huntingtons disease and the huntingtin protein. *Prog Mol Biol Transl Sci*, 107:189–214, 2012.

[23] Reiner A, Dragatsis I, Dietrich P. Genetics and neuropathology of huntingtons disease. *Int Rev Neurobiol*, 98:325–72, 2011.

[24] Duyao M, Ambrose C, Myers R et al. Trinucleotide repeat length instability and age of onset in huntingtons disease. *Nat Genet*, 4:387–92, 1993.

[25] Novak MJ, Tabrizi SJ. Huntingtons disease. *BMJ*, 340:c3109, 2010.

[26] Vonsattel JP, Myers RH, Stevens TJ et al. Neuropathological classification of huntingtons disease. *J Neuropathol Exp Neurol*, 44:559–77, 1985.

[27] Bohanna I, Georgiou-Karistianis N, Hannan AJ et al. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for huntingtons disease. *Brain Res Rev*, 58:209–25, 2008.

[28] van den Bogaard S, Dumas E, van der Grond J et al. Mri biomarkers in huntingtons disease. *Front Biosci (Elite Ed)*, 4:1910–25, 2012.

[29] van den Bogaard SJ, Dumas EM, Acharya TP et al. Early atrophy of pallidum and accumbens nucleus in huntingtons disease. *J Neurol*, 258:412–20, 2010.

[30] Rosas HD, Hevelone ND, Zaleta AK et al. Regional cortical thinning in preclinical huntingtons disease and its relationship to cognition. *Neurology*, 65:745–47, 2005.

[31] Wolf RC, Gron G, Sambataro D et al. Brain activation and functional connectivity in premanifest huntingtons disease during states of intrinsic and phasic alertness. *Hum Brain Mapp*, 33:2161–73, 2012.

[32] Kloppel S, Henley SM, Hobbs NZ et al. Magnetic resonance imaging of huntingtons disease: preparing for clinical trials. *Neurosci*, 164:205–19, 2009.

[33] Paulsen JS, Magnotta VA, Mikos AE et al. Brain structure in preclinical huntingtons disease. *Biol Psychiatry*, 59:57–63, 2006.

[34] McDermott LM, Ebmeier KP. A meta–analysis of depression severity and cognitive function. *J Affect Disord*, 119:1–8, 2009.

[35] Poletti M, de Rosa RA, Bonucelli U. Affective symptoms and cognitive functions in parkinson's disease. *J Neurol Sci*, 317:97–102, 2012.