Summary

Huntingtons disease (HD) is an autosomal neurodegenerative disorder caused by the expansion of the huntingtin gene located on chromosome 4. The clinical picture is characterized by a triad of symptoms: motor disturbances, behavioural changes and cognitive decline. Disease manifestation occurs in mid-life, having a devastating effect on an individuals work, family and personal life. To date, no means of curing or even slowing the disease are available and inheriting the gene inevitable leads to disease and a premature death. With the chromosomal mapping of the disease in 1983 and the discovery of the huntingtin gene in 1993, it became possible to be tested for the presence of the gene. When tested positive, and without overt signs and symptoms of the disease, an individual is called a premanifest gene carrier. In these premanifest gene carriers subtle changes in motor, behavioural and cognitive functioning have been found, along with early changes in structure and function of the brain.

Even though almost all cognitive tests require some form of motor response, often by means of written or verbal answers, there is little attention for the influence of motor functioning on cognitive test outcome in HD. Furthermore, because it is known that subtle motor deficits can occur in the premanifest phase of HD, understanding the possible negative effect of motor on cognitive functioning is necessary when trying to understand the progression of cognitive decline in all stages of HD.

In this thesis we have studied cognitive functioning in both patients and premanifest gene carriers, making use of several different techniques. Furthermore, we have investigated the influence of the known (subtle) motor deficits on cognitive scores by controlling for several measures of motor functioning.

The event related potential (ERP) P300, a positive peak visible on the EEG approximately 300 milliseconds following the presentation of a stimulus, is thought to be a neurophysiologic measure of attentional processing. The peak latency is hypothesized to be linked to speed of stimulus evaluation, or more generally, to speed of attentional processing, and its amplitude to the amount of attention allocated to the stimulus. A key feature of the P300 is that it is a measure of

attentional processing that is independent of motor influences. We have registered the P300 simultaneous to a test of attention, the Sustained Attention to Response task (SART) (**chapter 2**). Seventeen patients, 12 premanifest gene carriers and 15 controls were assessed. We found attentional control to be deficient in patients, as demonstrated by more errors being made by this group. Further investigation revealed post-error slowing in case of a certain type of error, which could be induced by a cognitive compensatory strategy called speed-accuracy trade-off. Furthermore, the observed attentional control deficits during the SART were corroborated by a reduced P300 amplitude and prolonged P300 latency, indicative of lowered attentional capacities.

The findings on the SART with simultaneous P300 registration were further studied in a longitudinal pilot-study (**chapter 3**). A subset of participants (five patients, nine premanifest gene carriers and 12 controls) from the cross-sectional study was also tested over a three year interval to investigate the progression of attentional control in HD. Patients showed heightened error rates and prolonged reaction times compared to the other two groups. There was however, no evidence for compensation in the form of speed-accuracy trade-off, as proposed in our cross-sectional study, because the slowing in reaction time did not prevent the occurrence of errors. One explanation that we offered was that due to disease progression the employment of the compensation strategy has reached a maximum in the patient group and is no longer effective in reducing error rates. On the other hand we observed slowing of reaction time on the trials just before having prevented an error in the premanifest gene carriers. As no slowing was found on other trials, and the slowing was not accompanied by elevated error rates, we hypothesized that compensatory mechanisms may be at work here.

The progression of cognitive functioning in the premanifest phase of HD was studied in a longitudinal study (**chapter 4**). The 29 premanifest gene carriers and 43 control participants who completed the seven-year follow-up were analyzed in this study. They were tested four times, using an extensive battery of tests covering most areas of cognitive functioning such as memory and executive functioning. We found that the premanifest gene carriers deteriorated on the domains of memory and concentration. These changes could primarily be ascribed to the carriers who converted to manifest disease over the study period. When these subjects were excluded from the analyses only the concentration sub test of the Wechsler Memory Scale was found to deteriorate over time for the premanifest gene carriers. We concluded that most cognitive change probably takes place in the phase close to disease onset.

Further study of this cohort resulted in an additional ten-year follow-up of patients and premanifest gene carriers (**chapter 5**). The tests used in this study were combined into four factors by means of factor analyses: three cognitive (global cog-

nition, executive functioning and memory) and one motor factor (motor speed). The progression of premanifest gene carriers (n=26), patients (n=19) and control subjects (n=87) over ten-years on the four factors was studied using multilevel regression analyses. The patients showed lower baseline scores compared with controls on all cognitive factors. When the converters were analyzed separately from the participants who remained premanifest during the whole follow-up, we found that only the converters deteriorated over time as compared with controls on the executive functioning + memory factors. Furthermore, when the premanifest group was divided in those close to and those far from expected disease onset, we observed a deterioration on the executive functioning factor for the subjects close to disease onset. We concluded that the executive functioning factor is most sensitive to premanifest cognitive progression, especially around disease onset. Another important outcome of this study was that the influence of motor functioning on cognitive test scores is substantial and should be taken into account in cognitive research in HD.

We also investigated the different cognitive and functional profiles between two motor subtypes of HD: predominantly choreatic HD and predominantly hypokinetic-rigid HD (**chapter 6**). We divided the subjects from the REGISTRY study database into the two motor types, which resulted in 528 choreatic and 432 hypokinetic-rigid subjects. Using regression analyses we found that the hypokinetic-rigid group performed worse on a measure of global functioning, as well as on several measures of cognitive functioning. As the analyses were controlled for age and disease duration, and because both groups were comparable considering use of neuroleptics, we concluded that different profiles exist between the two motor types of HD. Here, predominantly choreatic HD subjects are functionally and cognitively better than predominantly hypokinetic-rigid HD subjects, which could have implications for both scientific research and clinical care.

To investigate the influence of motor functioning on cognitive functioning we designed an extra condition that measures motor functioning for two tests of executive functioning (the symbol digit modalities test [SDMT] and the figure fluency test [FFT]) (**chapter 7**). Subsequently we subtracted the motor condition from the original test score, which we hypothesized would result in a more pure cognitive score. Forty patients and 21 premanifest gene carriers were compared to 28 control subjects. We found a substantial negative influence of motor functioning on executive task performance, especially in patients. However, even in the premanifest group there motor disturbances were measurable. With the isolation of the actual cognitive component we found deterioration on the SDMT only, caused by deteriorating scores of subjects that were close to their predicted age at disease onset.

A general discussion and future perspectives are discussed (**chapter 8**). In sum-

mary, we advocate that the domain of executive functioning is best targeted in future clinical trials as this cognitive domain is most sensitive to premanifest change. The SDMT is recommended as a suitable executive test to serve as outcome measure. As most rapid deterioration of executive functioning is found in subjects approaching their clinical disease onset, this group is put forward as key research group in clinical trials. Following our findings of substantial negative effects of motor functioning on cognition, we advise future cognitive studies to always control for motor functioning in cognitive testing, to be able to entangle the influence of motor disturbances on cognition in HD. Lastly, the existence of two different HD motor phenotypes, namely predominant choreatic and predominant hypokinetic-rigid HD, with different clinical profiles brings about implications for both clinical care and scientific research.