Chapter 8

General discussion and future perspectives

Understanding the course of cognitive decline is of great importance in the study of HD, to gain knowledge to improve specialized care for HD patients and to aid the design of future clinical trials. Research in the premanifest phase of the disease is of particular importance as many pathophysiological mechanisms remain unclear. Furthermore, investigation of the influence that HD motor disturbances have on cognitive test results will help to entangle the actual cognitive effect from other influential factors.

Course of cognitive functioning

Impaired cognitive abilities such as mnestic deficits and executive dysfunctioning have consistently been found in manifest HD[1]. However, the results in the premanifest phase are not that clear-cut. Several longitudinal studies on cognition show cognitive deficits in premanifest gene carriers even decades before estimated age at disease onset[2], while others do not detect differences between their premanifest and control groups[3 4]. With the ever growing understanding of HD genetics we move closer to clinical intervention studies to investigate agents with possible disease modifying or disease slowing effects. Increasing the knowledge about phenotypical progression of symptoms remains however important as there is not yet a uniform agreement, especially in the areas of cognition and psychiatry.

Executive functioning most sensitive to premanifest change
In our cognitive studies we have found strong evidence that the cognitive domain of executive functioning is most sensitive to premanifest cognitive deterioration.

Ten-year follow-up of cognition (**chapter 5**) showed that the executive functioning factor was the only factor to show results in the premanifest group. Interestingly, when studying the premanifest group as a whole, results were not different from that of controls. Only when the subjects who converted to manifest disease over the ten-year follow-up were analysed separately from the subjects who remained premanifest during the study, informative differences emerged. The converters showed a significant deterioration over time compared with the control subjects, while the scores of the continual premanifest subjects were comparable to control scores. Likewise, when we divided the premanifest group into those subjects who at baseline were far from expected disease onset and those who were close to onset, only the subjects close to expected onset showed lower baseline scores compared to controls, on the executive functioning factor only.
Further analyses revealed that the above findings were the result of poorer performance of the converter and close to onset groups on the Symbol Digit Modalities test (SDMT). Large premanifest effects on the SDMT were also found in our one-year follow-up study where we tested possible decline on both the SDMT and the Figure Fluency test (**chapter 7**). Even when we controlled for the influence of motor functioning, only the SDMT proved sensitive to premanifest change in the close to predicted onset group. The SDMT is a widely used test of executive functioning, and has often been found to be sensitive to change in the premanifest phase of HD. Our results support other findings that the SDMT is a well suited cognitive instrument to catch early cognitive decline in HD.

The above results lead us to hypothesize that progression of executive functioning in the premanifest phase evolves in a non-linear manner. Subjects that are further away from disease onset are able to maintain test requirements to the level of controls, while subjects close to disease onset show a rapid decline in performance. Additionally, the lack of deterioration over time for the manifest group suggests that most rapid deterioration of executive functioning abilities occurs around disease onset. Furthermore, in our study on cognition over a seven-year follow-up period (**chapter 4**) we found additional evidence for non-linear decline of memory functioning. Here, the observed memory decline over time in the premanifest group could be fully attributed to the gene carriers who converted to manifest disease over the follow-up time. Premanifest subjects who remained without clinical motor symptoms did not show memory deficits compared to controls, they only showed lower scores on a sub-test supposed to measure concentration abilities. That progression of cognitive symptoms does not evolve in a linear manner has also been reported by other authors. Snowden et al.[5] and Paulsen et al.[2] have both observed a more rapid decline of memory and executive functioning, respectively, in subjects approaching motor symptomatic disease onset, as compared to gene carriers further away from disease onset. Furthermore, Rupp et al. have reported on a longitudinal study where those closest to onset showed the largest rates of decline on cognitive measures[6].

Evidence for compensatory mechanisms

In this thesis we provide evidence for possible cognitive compensatory mechanisms in HD. In the cross-sectional study on the SART and simultaneous P300 registration (**chapter 2**) we observed a pronounced post-error slowing of reaction time for the manifest HD group, which could be indicative of a compensatory strategy to prevent the occurrence of errors. This so-called 'speed accuracy trade-off', where a slowing in reaction time raises the amount of correct responses, could be an explanation for our findings. The slowing indeed seems to prevent the manifest HD group from making more No-go errors compared to both premanifest gene carriers and controls. The post-error slowing that we observed could not be ascribed to mere motor slowing. Indeed, the manifest group was slower to react to the appearance of stimuli overall. For the reaction time pattern of trials surrounding correctly responded No-go trials a significantly slower but similar pattern of reaction was observed for the manifest group compared to the premanifest gene carriers and the controls. However, when studying the pattern around incorrectly responded No-go trials, the responses were not only slower, but a different pattern also emerged. The difference in reaction time patterns surrounding correct No-go trials and No-go trials where an error has been made, leads us to hypothesize that the observed post-error slowing can indeed be caused by a compensatory mechanism such as speed accuracy trade-off.

In the longitudinal study on the SART and P300 (**chapter 3**) we no longer found evidence for compensation in the manifest group. Manifest subjects showed slower responses compared to premanifest gene carriers and controls, and also slowed more over time compared to both other groups. As there was no observed benefit from the slowing (i.e. less errors), we assumed that in this group of patients the neurodegenerative damage has become too large to effectively apply compensatory strategies. In contrast, we did find evidence for compensation taking place in our premanifest group. Only on specific trials we found a slowing over time in this group, and as there was no increase in errors over time, we hypothesized that this could reflect the implementation of the compensatory speed accuracy trade-off strategy.

That compensatory mechanism are at work in HD, and especially in the premanifest phase of the disease, is an idea that is receiving growing evidence. Using functional MRI, both cognitive[7] and motoric[8] compensation has been reported, as well as cognitive compensation using event related potentials[9]. In other neurodegenerative diseases such as Parkinson's and Alzheimer's disease compensatory mechanisms have also been found, sometimes referred to as the "cognitive reserve hypothesis". Furthermore, the unexpected lack of functional changes in premanifest gene carriers in the TRACK-HD study has resulted in the TRACK-ON HD study, especially designed to investigate possible compensatory mechanisms in the premanifest phase of HD.

Influence of motor functioning on cognition

HD is primarily known as a movement disorder, and clinical disease onset is in most cases based on the appearance of motor symptoms characteristic for the disorder. However, subtle disturbances in motor functioning have also already been found in premanifest subjects[10]. And as almost all cognitive tests require some kind of motoric response, often by means of verbal or written answers, investigating the influence of motor changes on cognitive functioning could provide important information on cognitive functioning.

Evidence for negative effect of motor on cognition
In our ten year longitudinal study on the course of cognition in HD (**chapter 5**) we investigated the influence of motor speed on cognition by adding this variable as a covariate in the cognitive statistical model. We found that the significant cognitive results diminished by 20% when motor speed was taken into account, opposed to the model without this motor measure. Here, several results that ceased to be significant, while those who remained significant lessened in strength. We concluded that motor speed has a substantial influence on cognitive test results, accounting for up to 20% of the significance of cognitive results when not statistically accounted for.
In another study we created additional conditions for existing cognitive tests of executive functioning, the SDMT and the Figure Fluency test (FFT) (**chapter 7**). These extra conditions were designed in such a way that the cognitive load was minimal while the motor demands were relatively similar to the original test. By subtracting this motor condition from the original test score we expected to measure a more 'pure' cognitive score. Our results showed there was a substantial (negative) influence of motor functioning on cognition, especially in the manifest HD group. When the actual cognitive component was isolated by subtraction of the motor component, no cognitive results remained for this group. For the premanifest group the influence of motor disturbances could also be detected, however, cognitive differences could still be measured. From these two studies we can conclude that the influence of motor functioning in HD has a negative effect on cognitive outcomes. Even in premanifest subjects, where motor disturbances are very subtle, cognitive outcomes are impacted by these abnormalities. Even though the motoric effect is substantial, we have also always measured a cognitive effect in premanifest subjects in both studies.

Two motor phenotypes with different clinical profiles
There is not only an influence of motor functioning on cognition, we have also found evidence for the existence of different motor subtypes of HD, with different cognitive profiles (**chapter 6**). When we divided a large group of manifest HD subjects into either choreatic or hypokinetic-rigid HD according to the motor signs that were predominant in these subjects, we found that the hypokinetic-rigid group

performed significantly worse on tests of global and cognitive functioning, compared with the choreatic group. Furthermore, we established that these differences were not caused by differences in age, disease duration and use of neuroleptic drugs, which strengthened our hypothesis that fundamental different clinical profiles exist between predominant choreatic and predominant hypokinetic-rigid HD.

Future perspectives

To date, many clinical trials investigating the efficacy of agents designed to enhance functioning in HD subjects are implemented in different stages of manifest disease. If we however want to move forward to disease modification or even prevention, inclusion of subjects in the premanifest phase is vital. Already a small number of clinical trials is aimed at preventative therapies in the premanifest phase (e.g. Pre-QUEST and PREQUEL [http://clinicaltrials.gov/ct2/home]), and the expectation is that this number will rise in the coming years. From our studies we can conclude that early changes in executive functioning are already visible in subjects nearing clinical onset, and that decline is rapid. Clinical trials investigating agents designed to improve cognitive functioning in HD should therefore make use of tests of executive functioning, preferably including the SDMT, to be best able to capture drug induced change.
Furthermore, our results prove that subjects close to their predicted disease onset are most suitable as key research group in future clinical trials. Firstly, as they show the most rapid decline in executive functioning opposed to premanifest subjects further from onset and subjects further into the manifest phase of HD, drug-induced disease modifying effects may potentially be measured over relatively short periods of follow-up time. Secondly, as they are the group to deteriorate most rapidly they are also the group that would probably show maximum benefit from drug intervention, especially when disease slowing agents will become available. Parallel to drug development projects, observational studies such as Track(-On) HD and Predict-HD are searching for the optimum time point in the course of HD to first introduce drug treatment. Our results on the course of cognition add to the knowledge from these multicentre studies.

To avoid overestimation of cognitive results we advocate that to control for a quantitative measure of motor functioning, such as reaction time, in cognitive studies, to be able to entangle the influence of motor influence on cognition in HD. Our findings also implicate that the results of previous cognitive studies which have not included some measure of motor functioning have to be interpreted with some caution. As a substantial part of the cognitive effect in these studies is possibly the result of (subtle) motor disturbances, the findings should not be regarded as 'pure' cognitive effects.

The existence of two different motor subtypes with different clinical profiles has implications for both care and scientific research. Concerning clinical care for HD patients, hypokinetic-rigid patients need more specialized care as they have been proven to be both generally and cognitively worse. Because a patient with predominant hypokinetic-rigid motor symptoms is more likely to have cognitive deficits, this patient is also more likely to benefit from repeated instructions, or cognitive training, to maintain a relatively good quality of life for a longer period of time. Instead, patients with predominant choreatic symptoms may need less cognitive care, even though they are often times motorically very affected.
The knowledge about different clinical profiles for patients with different predominant motor symptoms is also of importance for the design of future clinical trials. Studies using cognitive or global functional (e.g. total functional capacity scale) outcome measures which have mostly included patients with predominant choreatic HD motor symptoms will show different results from when mostly predominant hypokinetic-rigid HD patients or even a mix of the two groups are included.

Limitations
One general point of caution has to be noted. In all of the studies included in this thesis we have made the division of premanifest or manifest according to a cut-off point of the score on the total motor score (TMS), the subscale of the Unified Huntington's Disease Rating Scale measuring motor functioning. It may well have been that certain subjects already experienced a non-motor clinical onset, such as severe cognitive impairment or behavioral disturbances. Indeed, Orth et al.[11] investigated age at onset in the REGISTRY study and found that out of the 423 subjects studied 28% (120) had a non-motor onset of disease. The motor-based division that we have used could have introduced a selection bias, where subjects who may have been manifest based on cognitive or psychiatric criteria, but were nonetheless included in the (motor)premanifest group, possibly confounding study results. We question if the TMS should continue to be used as golden standard for group division in HD. Studies using broader criteria to make a distinction between manifest and premanifest may maximize both study and treatment outcomes.
Furthermore, it should be mentioned that the studies reported in this manuscript show some overlap in participants. A group of subjects (n=26) who participated in the longitudinal study on P300 and SART performance also participated in the seven and ten year cognitive follow-up study. Also, for the one-year follow-up study on executive functioning in both premanifest and manifest HD 15 subjects already also already participated in the seven and ten year follow-up study. This raises the question of practice effects, a well-known challenge in HD research. Due to the relative rarity of the disease HD subjects are often recruited for multiple studies using identical tests. This also makes that the results from the mentioned studies are not fully independent, which potentially limits generalizability.

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