Huntington's disease: cognition and apathy

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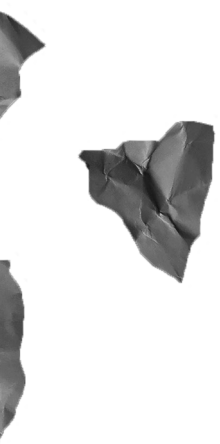

Chapter 7
Discussion and concluding remarks

The general aim of this thesis was to gain further insight into the cognitive profile and apathy in Huntington's disease (HD). This information is particularly useful to optimize clinical care and to aid the design of future clinical trials.

Cognitive profile

For research purposes it is common that HDGECs are grouped according to absence (i.e. pre-motormanifest) or presence (i.e. motormanifest) of motor symptoms. First, we evaluated whether this commonly used participant classification makes a useful distinction between HDGECs and whether these groups are homogeneous, especially in light of cognition. An overview of the participants' characteristics of the largest REGISTRY center was given by using different classifications (**chapter 2**). When dividing our cohort of 487 HDGECs according to absence and presence of motor symptoms, about 20% of the pre-motormanifest individuals were already clinically diagnosed based on cognitive and/or psychiatric symptoms. This leads to the conclusion that cognitive decline starts before motor symptoms are present and that these symptoms are clinically severe enough to diagnose individuals with HD without any motor symptoms. This is in line with previous research[1-4]. These results emphasize that the recently published guidelines, which state that HD diagnosis can be given purely on cognitive and/or psychiatric symptoms[5], fulfill a real need. In order to understand how this early cognitive decline further develops throughout disease progression, we used the entire REGISTRY cohort with the aim of mapping the cognitive profile throughout all disease stages (**chapter 3**). We found that significant cognitive decline is present even in the pre-motormanifest stages, which again leads to the conclusion that cognitive decline is often present before motor symptoms are apparent. In our study, tasks measuring psychomotor speed with low motor component, i.e. Stroop Word and Color test, were sensitive in detecting early cognitive decline, as well as tracking this decline throughout the later stages of the disease. Thus, psychomotor tasks are suitable for tracking cognitive abilities over time in HD.

We do not know why cognitive decline starts early in the course of their disease for some individuals and also, we do not understand the different rates of decline. Why do some patients progress much faster than others? In general, we do know that CAG length influences disease progression as has been shown for motor function, total functional capacity and atrophy in the brain[6, 7]. Therefore, we evaluated whether cognitive decline is also mediated by CAG length (**chapter 3**). Indeed, our results show that individuals with longer CAG lengths have a more rapid cognitive decline. This is not surprising as cognitive deficits are associated with changes in the brain and

this neurodegenerative process in the brain itself is mediated by CAG length. Thus, it seems logical that CAG mediates cognitive performance. CAG length is a disease specific factor which influences cognitive decline but there might be other factors influencing cognitive performance. As there is no cure for HD, many HDGECs take symptomatic medication. Therefore, we explored whether there is a difference in cognitive performance between HDGECs taking medication targeting non-cognitive neuropsychiatric signs and/or tetrabenazine and non-users (**chapter 4**). First, we have shown that symptom management is common in HD: about 42% of all REGISTRY participants used one or more of the predefined drugs; benzodiazepines, selective serotonin reuptake inhibitor (SSRI) antidepressants, antipsychotics, atypical antipsychotics or tetrabenazine. Medication use gradually increased from pre-motormanifest participants (12%) to late stage manifest participants (81%) and polypharmacy also increased from 3% to 48%. However, the only effect found in our study was a negative effect of using antipsychotic on cognitive performance in the early HD stages. We did not find any effects of using benzodiazepine, SSRIs, atypical antipsychotics and tetrabenazine on cognitive performance in the real-life medication use at the clinics. A major limitation of this study is that we used relatively broad medication categorization and that this could mask effects of any one particular drug. But at least, this study shows the groups effect of real-life medication use on cognitive performance. Concluding, group analysis did not show medication to have a significant effect on cognitive performance, except for antipsychotics.

Apathy

The behavioral symptoms in HD are diverse[8]. Apathy is common, is the only behavioral symptom closely related to disease progression[9-11] and is present in almost all late stage HDGECs[11]. Apathy is defined as 'lack of motivation resulting in diminished goal-directed behavior, cognition, and emotion'[12] and, in general, is associated with a disruption of the prefrontal cortex - basal ganglia circuit[13]. Therefore, we aimed to find a relationship between apathy and the neurodegenerative process in HD (**chapter 5**). Our results are in line with previous studies that apathy is common and can already be present in the pre-motormanifest stage. In addition, we have shown that that atrophy of the thalamus is associated with apathy leading us to conclude that also in HD apathy is associated with a disruption of the prefrontal cortex – basal ganglia circuit. However, no other subcortical structure was found to be associated with apathy. Very recently one study found that the prefrontal cortex is associated with apathy in HD[14], the prefrontal cortex – basal ganglia circuit is indeed disrupted in HD but the

prefrontal cortex is associated with developing apathy in HD rather than subcortical structures.

Some studies have shown that HDGECs are unaware of their symptoms, including their behavioral symptoms[15, 16]. Therefore, we evaluated whether HDGECs and their proxies agree on the degree of apathy by using a self-report questionnaire (**chapter 6**). As mentioned, apathy can already be present in pre-motormanifest individuals, the incident and severity rate drastically increase from the early HD stage to the late motormanifest stages. Overall, proxies and HDGECs agree on the degree of apathy. In the pre-motormanifest stage HDGECs even report more apathy than their proxies, although the overall degree of apathy is generally low in this stage. However, it could be the case that pre-motormanifest HDGECs are more aware of internal changes than their proxies.

Concluding remarks

Over the recent years a unique situation has arisen for HDGECs, as several clinical trials were set up to evaluate medication for symptomatic treatment[17]. Very recently, one trial has been launched which aims to lower the huntingtin level in the brain to stop or delay the neurogenerative process[18]. Many trials have been set up and there are some promising studies, but nothing has been proven yet. And even more studies are at the horizon. With the results of our work we can advise to include executive function (especially psychomotor speed) in the battery when cognition is being studied. At the moment, no threshold is known at which to conclude that cognitive impairment (due to HD) has started. When it comes to evaluating cognition, we would favor to group participants according to age and CAG length rather than on presence and absence of motor symptoms. In addition, we have shown that medication targeting non-cognitive neuropsychiatric disturbances and tetrabenazine might not have such an enormous influence on cognitive outcome as previously assumed, when groups are analyzed. We think that exclusion criteria based on medication use should be carefully evaluated, as in group analysis the individual usage of certain medication might not make much difference. Of course, on individual basis these medications can have side effects which should be carefully evaluated and if necessary be replace by other medication.

Considering that executive dysfunction and apathy seem to be closely related, we would advise to also evaluate apathy in a standardized way when cognition is measured in a clinical trial. If an agent under investigation is supposed to have effect on the prefrontal cortex, it might also positively affect apathy.

The HD community hopes that an intervention which slows or stops the disease progression will be found soon. And our results help to at least shape those studies to be able to evaluate a possible effect.

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