UNIVERSITY OF COPENHAGEN
FACULTY OF SOCIAL SCIENCE

APATHY, SOCIAL COGNITION, AND SELF-PERCEPTION

ASSESSING NEUROPSYCHOLOGICAL FACTORS IN HUNTINGTON'S DISEASE

PhD Thesis

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To my family

Kristoffer, Agnes, Hana, and Eva

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I Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers. Cognitive and Behavioral Neurology, 34(4), 295–302. https://doi.org/10.1097/WNN.0000000000000286

II Hendel R. K., Hellem M. N. N., Hjermind L. E., Nielsen J. E., & Vogel A. (2022). On the association between apathy and deficits of social cognition and executive functions in Huntington's Disease. Journal of the International Neuropsychological Society. Early Access. https://doi.org/10.1017/S1355617722000364

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III Hendel, R. K., Hellem, M. N. N., Larsen, I. U., Vinther-Jensen, T., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2022). Impairments of social cognition significantly predict the progression of functional decline in Huntington's disease: A 6-year follow-up study. Applied Neuropsychology: Adult. Early Access. https://doi.org/10.1080/23279095.2022.2073824

STUDY III: CHANGES IN THE SELF-PERCEPTION OF AUTONOMY

IV Hendel R. K., Hellem M. N. N., Hjermind L. E., Nielsen J. E., & Vogel A. (2022). An Exploratory Study Investigating Autonomy in Huntington Disease Gene Expansion Carriers. Journal of Huntington's Disease. Early Access. https://doi.org/10.3233/JHD-220540

Preface

This PhD project took place at the Danish Dementia Research Centre and the Memory Clinic at Rigshospitalet from year 2018-2022. The project was generously supported by the Danish Huntington's Disease Association Research Fund; the A.P. Møller Foundation for the Advancement of Medical Science; the Søren Segel & Johanne Wiibro Segel's Research Fund; The Novo Nordisk Foundation; and the Research Board at Rigshospitalet.

I have always felt proud of being a part of the Danish Dementia Research Centre. Under the leadership of *Gunhild Waldemar,* the Centre has had and still has a great impact and importance for the research community and for the public. This project would not have been possible without the time and energy used by all the participants. I truly admire your commitment to the research community. Thank you all very much for your contributions to this project. I sincerely hope that the results of my research will be of use to you and your families.

For my stay abroad, I received a warm welcome at the Translational Neuroendocrine Research Unit and the Huntingtoncentrum at Lund University in April 2022. Thank you *Åsa Petersén* for a great experience in an international setting.

To my primary supervisor, *Asmus Vogel,* thank you for always believing in me. You have pushed me to evolve during this project and I have enjoyed our collaboration every step of the way. To my supervisor, *Lena E. Hjermind*, thank you for all your encouragements and for helping where possible. I really admire your dedicated patient care and I have appreciated the opportunity to draw on your extensive knowledge about Huntington's disease. And to my supervisor, *Jørgen E. Nielsen*, thank you for your calm attitude and confidence in my work and for using your overwhelming knowledge to put our results into a greater perspective.

Marie N. N. Hellem, you have been my closest colleague during this project. I am grateful to have shared this project with you. You have become much more than a colleague to me, and I have enjoyed our friendship during the past years – with hopefully much more to come.

To all my neuropsychological colleagues, thank you for your encouragements and your interest in my project. I have appreciated being part of such a professional group of neuropsychologists and I hope to have the opportunity to work with you again in the future.

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And finally, a special thank you to my husband *Kristoffer* for letting me draw on your extensive competence and academic experience. It has been an enormous help knowing that I could always ask for your advice. You are the most reflective person I know and I love you with all my heart.

REBECCA, AUGUST 2022

List of Abbreviations

ACS-30	Autonomy-Connectedness Scale
CAG	cytosine-adenine-guanine
CAP	CAG Age Product
EH	Emotion Hexagon
HAM-17	Hamilton's Depression Scale
HD	Huntington's disease
IAF	Index of Autonomous Functioning
LARS	The Lille Apathy Rating Scale
mHTT	mutant Huntingtin protein
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
PBA-s	The short Problem Behavior Assessment for Huntington's Disease
RMET	Reading the Minds in the Eyes Test
SCL-90-R	Symptom Checklist 90 Revised
SDMT	Symbol Digit Modality Test
SI-M	Social Inference Minimal
TASIT	The Awareness of Social Inference Test
TFC	Total Functional Capacity
TMS	Total Motor Score
TMT B	Trail Making Test B
UHDRS	Unified Huntington's Disease Rating Scale

A note on abbreviations. Abbreviations will only be applied for expressions used often in the text apart from abbreviations typical for the field of research, like cytosine-adenine-guanine (CAG). The abbreviations will be defined when first presented in every section to improve readability.

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Summary

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease, classically characterised by motor disturbances, cognitive impairments, and psychiatric illnesses, but which most often also include behavioural symptoms and disturbances of the autonomous nervous system (McColgan & Tabrizi, 2018; Roos, 2010, 2014). Cognitive and behavioural deficits have been identified as some of the most devastating symptoms of HD, which places the greatest burden on the HD families (Paulsen et al., 2017). It can be suggested that these deficits are specifically burdensome since they affect the personal character of the individuals with the disease.

The aim of this PhD project was to examine changes in self-perception, cognition, and behaviour of individuals with HD. These symptoms are thought to lead to a higher caregiver burden and a higher degree of distress. The project focused on three symptom groups: apathy, social cognitive dysfunction, and changes in the self-perception of autonomy. The project assessed a large well-defined single-site cohort of HD gene expansion carriers and gene-negative family-based controls, some of which had been assessed previously in year 2012-2013. The cohort of year 2017-2021 was comprised of follow-up participants as well as newly enrolled participants. A total of 108 HD gene expansion carriers and 32 gene-negative family-based controls were included in the project.

The results from the present project demonstrates changes in self-perception, cognition, and behaviour in individuals with HD. Both specific deficits measured by quantitative psychological instruments like apathy and social cognitive dysfunction, as well as changes in the perception of self of the HD gene expansion carrier were affected by the disease. These changes are most prevalent in the motor-manifest stage of disease. The studies showed that the motor-manifest HD gene expansion carriers had a significantly higher degree of apathy, characterised by the subtypes Intellectual Curiosity and Action Initiation, when compared to premanifest HD gene expansion carriers and controls. Apathy was associated with motor disturbances and symptoms of depression, while cognitive dysfunction did not have an impact on the degree of apathy. The HD gene expansion carriers who were impaired on the domain of *social cognition* were significantly different from the HD gene expansion carriers who were impaired on the *executive function*s domain. Impairments on the domain of *social cognition* and motor disturbances significantly predicted the decline in functional capacity across the 6-years of follow-up. Finally, a significant lower degree on some aspects of autonomy was found in motor-manifest HD gene expansion carriers. One subscale of autonomy was associated with apathy, but no other associations were found between the self-perception of autonomy and motor function, cognitive status, or neuropsychiatric illnesses.

A comprehensive description of the deficits that reflects changes in self-perception, cognition, and behaviour can hopefully contribute to the knowledge on how HD can affect the person with the disease. Ultimately, the knowledge from this project can contribute with a better understanding of the invasiveness of these symptoms and in turn to better psychoeducation of families with HD.

Dansk Resumé | Danish Summary

Huntingtons sygdom er en dominant arvelig neurodegenerativ sygdom, som klassisk er karakteriseret ved motoriske symptomer, kognitive forstyrrelser og psykiatriske lidelser, men som oftest også inkluderer adfærds forstyrrelser og ændringer i det autonome nervesystem (McColgan & Tabrizi, 2018; Roos, 2010, 2014). Det er påvist at kognitive og adfærdsmæssige forstyrrelser er nogle af de mest invasive symptomer ved HD, som leder til den største byrde for familier med HD (Paulsen et al., 2017). Det kan formodes at disse forstyrrelser er specielt belastende idet de påvirker personen med sygdommen og reflekterer ændringer af den personlige karakter hos individer med HD.

Formålet med dette Ph.d.-projekt var at undersøge ændringer i selvopfattelse, kognition og adfærd hos individer med HD. Disse symptomer kan antages at lede til en højere grad af stress hos de pårørende. Projektet fokuserede på tre symptom grupper: apati, social kognitive forstyrrelser og ændringer i selvopfattelsen af autonomi. Projektet inkluderede en stor veldefineret kohorte af HD genbærere og gen-negative familie kontroller, hvoraf nogle blev fulgt op efter tidligere undersøgelser i år 2012-2013. Kohorten fra år 2017-2021 bestod af opfølgningsdeltagere og ny-inkluderede deltagere. Totalt blev 108 HD genbærere og 32 gen-negative familie kontroller inkluderet i projektet.

Resultaterne fra dette projekt demonstrerer at HD kan lede til ændringer selvopfattelse, kognition og adfærd hos individer med HD. Både specifikke forstyrrelser målt med kvantitative psykologiske instrumenter, som apati og social kognitive forstyrrelser, samt ændringer i opfattelsen af selvet hos HD genbærere er påvirkede af sygdommen. Disse ændringer er mest fremtrædende i det motor-manifeste stadie af sygdommen. Studierne viste at motor-manifeste HD genbærere havde en signifikant højere grad af apati, karakteriseret ved subtyperne Intellektuel Nysgerrighed og Handlings Initiering, sammenlignet med præmanifest HD genbærere og kontroller. Graden af apati var associeret med de motoriske forstyrrelser og depressive symptomer, mens kognitiv dysfunktion ikke havde nogen indvirkning på graden af apati. De HD genbærere som var nedsat på domænet *social kognition*, var signifikant forskellige fra de HD genbærere, som var nedsat på domænet *eksekutive funktione*r. Forstyrrelser på domænet *social kognition* og motoriske forstyrrelser kunne prædiktere nedgangen i funktionel kapacitet over den 6 år lange opfølgningsperiode. En signifikant lavere grad af nogle aspekter af autonomi blev identificeret hos motor-manifeste HD genbærere. En subskala af autonomi blev associeret med apati, mens selvopfattelsen af autonomi ikke var associeret med motor funktion, kognitiv status eller neuropsykiatriske lidelser.

En fyldestgørende beskrivelse af forstyrrelser som reflekterer ændringer selvopfattelse, kognition og adfærd kan forhåbentlig bidrage med bedre viden om, hvordan HD påvirker personen med sygdommen. Resultaterne fra dette projekt kan bidrage til en bedre forståelse af hvor indgribende disse symptomer kan være og til en bedre psykoedukation for familier med HD.

Background

This PhD thesis focuses on changes in self-perception, cognition, and behaviour in individuals with Huntington's disease. In this section, background information on Huntington's disease will be presented, followed by an introduction to the central symptom groups of the thesis: symptoms of apathy, social cognitive dysfunction, and changes in autonomy.

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease caused by a prolonged trinucleotide cytosine-adenine-guanine (CAG) expansion in the DNA of chromosome 4 (McColgan & Tabrizi, 2018; Ross et al., 2014; The Huntington's Disease Collaborative Research Group, 1993; Walker, 2007). The prevalence of HD in caucasians is 4-12.4:100.000, while in Denmark it has been found to be 5-8:100.000 (Evans et al., 2013; Gilling et al., 2017; Rawlins, 2010; Roos, 2010). HD is a multifaceted disease classically presenting with a triad of symptoms: motor disturbances, cognitive impairments, and psychiatric illnesses. These cardinal features are often accompanied by behavioural symptoms as well as weight loss, sleep disturbances, and abnormal functions of the autonomous nervous system (Roos, 2010, 2014). No formal treatment of HD exists and the disease will ultimately lead to consecutive functional decline until death about 15-20 years after initial diagnosis, primarily due to pneumonia or heart disease (Bunner & Rebec, 2016; Roos, 2010).

Cardinal features

Motor Disturbances The motor disturbances in HD can be divided into hyper- and hypokinetic movements. Chorea is the most characteristic of the hyperkinetic symptoms with dance-like, rapid, short-lasting, involuntary movements of the trunk, face, and extremities (Roos, 2014). Other hyperkinetic movements include tremor and tics (Bunner & Rebec, 2016; Roos, 2014). The hypokinetic movements are characterised by incoordination, dystonia, rigidity, akinesia and bradykinesia, balance, and gait disturbances (McColgan & Tabrizi, 2018; Roos, 2014; Ross et al., 2014). With time, the choreatic symptoms become increasingly less prominent, whereas the hypokinetic movements are exacerbated as the disease progresses, leading to overall more slow and rigid movement patterns (Jacobs et al., 2016; Roos, 2014).

Cognitive Impairments One of the earliest and most common cognitive deficits affecting individuals with HD is psychomotor slowing (Cavallo et al., 2022; Craufurd & Snowden, 2014). Psychomotor slowing is a selective cognitive symptom occurring in the premanifest stage of disease whereafter it gradually decreases throughout the disease progression with a linear trend of decline (Paulsen et al., 2017). Executive dysfunction and attentional deficits are two of the most prominent cognitive symptoms of the disease affecting most individuals in the early stages of HD (Cavallo et al., 2022; Snowden, 2017). Executive dysfunction is closely related to almost all other cognitive impairments described in HD (Paulsen et al., 2017), but atrophy affecting executive functions might be delayed or slowed by cognitive reserve (Bonner-Jackson et al., 2013). Other cognitive symptoms include visuo-spatial and -constructive disabilities, compromised language abilities with slow

retrieval of words, restricted fluency, simplified utterances, and memory problems, expressed as absent-mindedness, caused by strategic and organizational failures in information acquisition and retrieval (Cavallo et al., 2022; Craufurd & Snowden, 2014; Snowden, 2017). Moreover, deficits in social cognition leads to compromised theory of mind and poor emotion recognition (Bora et al., 2016; Snowden, 2017). Impaired emotional expressions are demonstrated as paralleling the deficits in emotion recognition, whereas the ability to understand and memorise emotions seems to be preserved (Paulsen et al., 2017; Trinkler et al., 2013).

Psychiatric Illnesses Patients suffering from HD are often diagnosed with psychiatric illnesses which can arise before the motor manifestation of the disease (Craufurd & Snowden, 2014; Thompson et al., 2012). Most common amongst these are depression and anxiety, with estimated prevalence rates of between 9–63% for depression and 17-61% for anxiety (Paoli et al., 2017). Irritability presents early and is characterized by intolerance, impatience, and poorly controlled anger that can lead to outbursts and violent behaviour. Other psychiatric symptoms that are prevalent in HD include isolated psychotic symptoms or schizophrenic symptoms like delusions and hallucinations, obsessive and perseverative behaviours, suicide ideation, and disorders of sexual behaviours like hypo- or hypersexuality (Craufurd & Snowden, 2014).

Genetics

In healthy individuals, the gene responsible for HD codes for the wild type huntingtin protein but in HD the expanded CAG repeat length results in an elongated polyglutamine stretch causing a mutated huntingtin protein (mHTT) (Bunner & Rebec, 2016; Ghosh & Tabrizi, 2018). A CAG repeat count of ≤ 26 is within normal variation, but in subjects carrying a CAG repeat length of ≥ 40, the gene has full penetrance and HD will develop at some point during their life (see figure 1). Reduced penetrance with 36-39 repeats may lead to HD in older age (Ghosh & Tabrizi, 2018; Rubinsztein et al., 1996). Intermediate allele carriers, with a CAG repeat length of between 27-35 repeats will not necessarily develop symptoms of the disease within their life span but have a risk of passing on the HD gene to their offspring (Bunner & Rebec, 2016; Ghosh & Tabrizi, 2018). The HD gene is inherited in an autosomal dominant fashion, where individuals with a parent affected

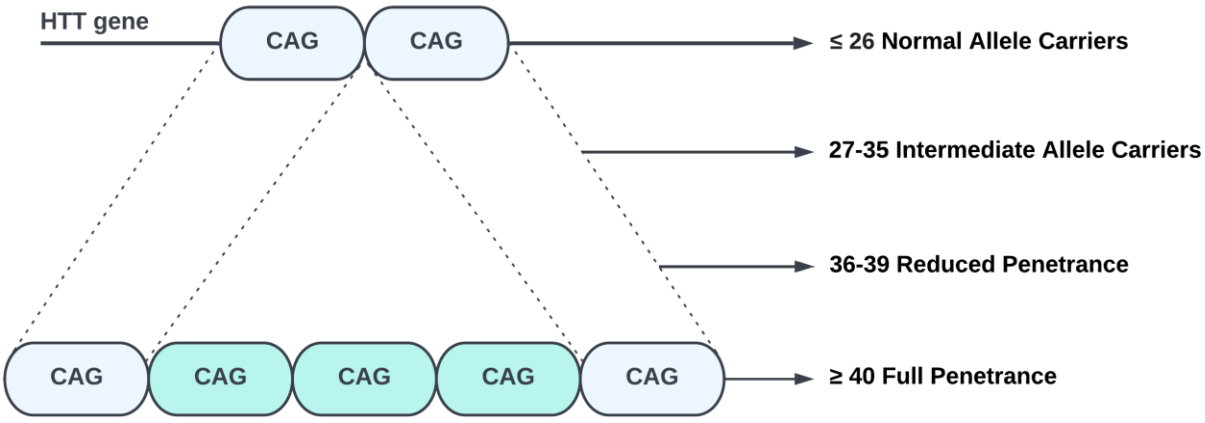

Figure 1. Overview of CAG repeat lengths on the HTT gene and penetrance of HD. The figure is modified from Chandra et al. (2014).

by HD have 50% risk of inheriting the gene. Generally, there is a wide variation in CAG repeat length with unstable intergenerational transmission. From paternal inheritance, the CAG repeat length can be affected by a larger increase in preceding generations due to an unstable germline inheritance – a process called anticipation (Gusella et al., 2014; Telenius et al., 1993).

Neuropathology

Neuron degeneration and dysfunction can be caused by abnormal accumulation of mHTT fragments but the mechanisms are not well understood (Ghosh & Tabrizi, 2018; Mehrabi et al., 2016; Waldvogel et al., 2014). One theory is that the aggregates of the mHTT make abnormal deposits in the nuclei, cytoplasm, dendrites, and axon terminals of the neurons, causing a pathogenic cascade ultimately leading to neuronal death. Atrophy caused by aggregated mHTT is most pronounced in striatal medium spiny neurons of the caudate and putamen and can be found in these areas decades before clinical diagnosis (Aylward et al., 2011; Bunner & Rebec, 2016; Scahill et al., 2017).

As the striatum is closely connected to the cerebral cortex through cortico-striatal projections, dysfunction of the cortico-basal ganglia connections can explain many of the symptoms that are seen in HD (Mehrabi et al., 2016). These include motor problems, cognitive dysfunction, and behavioural symptoms (Bunner & Rebec, 2016; Mehrabi et al., 2016).

Disease onset

Most HD gene expansion carriers are diagnosed with manifest HD in their midlife, at 40–50 years of age (Bunner & Rebec, 2016). An HD diagnosis is based on the diagnostic certainty of motor disturbances affecting the individual (Ross et al., 2014). Interestingly, numerous studies have demonstrated that cognitive and psychiatric symptoms can precede the motor diagnosis for more than a decade (Epping et al., 2016; Paulsen et al., 2013, 2017; Vinther-Jensen et al., 2014). The age at disease onset can be partly predicted by the CAG repeat length, where a longer repeat length predicts an earlier manifestation of disease. Several predictive models of age at onset have been proposed. The CAG-age-product (CAP) score was the first model for the age at onset and is thought of as a disease burden score (Penney et al., 1997). The CAP score is based on a cumulative measure of the toxic mHTT protein, but is not recommended for use in the clinic. While the CAG repeat length can be predictive of the disease onset, specifically in terms of motor and cognitive symptoms, the duration of disease and psychiatric symptoms seems to be independent of the CAG repeat length (Gusella et al., 2014).

Natural history

The disease course has been examined in large multi-site longitudinal cohort studies, from where evidence on the earliest changes have been demonstrated, including impairments and disturbances characterising proximity to diagnosis, and symptoms predictive of progression. Despite wide variability between patients, such studies can help illustrate the classical course of the disease. The most well-known studies are the Neurobiological Predictors of Huntington's Disease (PREDICT-HD) and the TRACK-HD (Paulsen et al., 2008, 2014; Tabrizi et al., 2009, 2011, 2012, 2013). These studies have described significant striatal volume loss, specifically in the putamen and caudate regions in the premanifest stage of disease, even 10-15 years prior to diagnosis (Aylward et al., 2011;

Paulsen et al., 2014; Ross et al., 2014; Tabrizi et al., 2011, 2012, 2013). Motor functions and functional capacity decrease throughout the premanifest stage, with an acceleration of motor disturbances just prior to diagnosis (Paulsen et al., 2014; Tabrizi et al., 2011, 2012, 2013). Psychiatric illnesses and cognitive dysfunction are present in premanifest HD gene expansion carriers and decline over time (Paulsen et al., 2014). The Symbol Digit Modality Test (SDMT) is the most sensitive cognitive measure and predictive of disease progression (Paulsen et al., 2013; Tabrizi et al., 2013). Emotion recognition abilities are significantly affected in the premanifest stage of disease and can differentiate between premanifest HD gene expansion carriers and manifest HD gene expansion carriers (Tabrizi et al., 2013). Symptoms of apathy are more prevalent in premanifest and manifest HD gene expansion carriers when compared to controls (Tabrizi et al., 2009). In manifest HD gene expansion carriers, whole-brain volume decreases over time and there is evidence of cortical thinning throughout the cortex (Tabrizi et al., 2009, 2013). Initial motor symptoms is predictive of later rapid functional decline in manifest HD (Tabrizi et al., 2013). Functional decline is further associated with frontal lope functions like apathy, irritability, and affect.

Introduction to the Studies

Some symptoms of Huntington's disease (HD) have a greater impact on the person living with the disease than others. While the motoric symptoms of HD might be easier to accept, research has demonstrated that the most debilitating symptoms are cognitive and behavioural, placing the greatest burden on HD families (Paulsen et al., 2017; Ready et al., 2008). These symptoms are highly associated with functional decline in HD and highly predictive of the motor diagnosis. It can be speculated that these symptoms are especially challenging for the patients and their families because they affect the personal character of individuals with HD. This project focuses on three symptom groups that reflects changes in self-perception, cognition, and behaviour: apathy, social cognitive dysfunction, and changes in autonomy.

STUDY I: CHARACTERISING APATHY IN HD

The underlying neuropathology of apathy, affecting the network of the limbic loop, might explain the frequent presence of apathy in HD (De Paepe et al., 2019; Le Heron et al., 2019; Levy & Dubois, 2006; Martínez-Horta et al., 2018). Apathy has been suggested to be present in up to 55-76% of patients with HD, with a longitudinal prevalence of up to 84-99% (Paulsen et al., 2001; Thompson et al., 2012; van Duijn et al., 2007). The presence of apathy follows the disease progression, with a higher frequency in more severe stages of disease (Camacho et al., 2018; Thompson et al., 2012). A substantive body of evidence have linked apathy to higher rates of functional decline (Fritz et al., 2018; Sellers et al., 2020; van Duijn et al., 2010), cognitive decline, specifically executive dysfunction (Andrews et al., 2020; Baudic et al., 2006; Reedeker et al., 2011; van Duijn et al., 2010), and depression (Andrews et al., 2020; Thompson et al., 2002; van Duijn et al., 2010). Depression and apathy share symptoms like inactivity, decreased response to others, and fatigue. However, depression and apathy can be present independently (Thompson et al., 2002), and depression involves specific symptoms like guilt, hopelessness, and sadness which is not typical in apathy and suggests a dissociation between the conditions (Lanctôt et al., 2017; Nobis & Husain, 2018).

Similarly, evidence on apathy has been demonstrated in other neurodegenerative diseases, with increased presence in severe stages of disease and close associations with cognitive dysfunctions and functional decline, specifically in Alzheimer's disease and Parkinson's disease (Dujardin et al., 2009; Fahed & Steffens, 2021; Manera et al., 2019; Nobis & Husain, 2018; Pagonabarraga et al., 2015; Radakovic & Abrahams, 2018).

Special interest should be directed at examining symptoms of apathy in HD, since apathy can lead to substantial caregiver burden and distress, as well as a lower quality of life for both patients and their caregivers (Craufurd et al., 2001; Fahed & Steffens, 2021; Manera et al., 2019; Nobis & Husain, 2018; Robert et al., 2018). In recent years, a greater focus on apathy has led to an understanding of apathy as a multidimensional syndrome encompassing different subtypes of emotion, social interaction, cognition, and initiation (Radakovic & Abrahams, 2018; Robert et al., 2018). While numerous instruments exist for the assessment of apathy, the most recent instruments are often based on the theoretic characterisation of apathy as a multidimensional

syndrome. In contrast, apathy is often characterised as a single behavioural symptom in HD literature, and substantial fractions of the available research characterises it as such by using the short Problem Behaviors Assessment for Huntington's Disease (PBA-s) for assessment (Craufurd et al., 2001). This is very likely one reason why apathy remains poorly understood in HD and why it remains unknown to what degree, evidence from other neurodegenerative diseases can apply to HD. A comprehensive assessment of apathy as a multidimensional syndrome is needed to characterise the specific types of apathy that are present in HD. Such evidence could also inform caregivers and families on the consequences that this syndrome can have and hopefully lead to a better understanding of the care needed by the patient and a lower burden on the caregivers.

STUDY II: SOCIAL COGNITIVE DYSFUNCTION AND FUNCTIONAL DECLINE

During the last decades, it has become well-known that social cognitive dysfunction is prevalent in HD (Bora et al., 2016; Snowden, 2017). Nonetheless, evidence on social cognitive dysfunction in HD is characterised by a simplified perspective on the social cognitive functions, with a specific focus on theory of mind and emotion recognition abilities and the use of a few specific tests for assessment (Bora et al., 2016). Social cognition includes several other functions such as sympathy, empathy, and alexithymia, which despite being highly relevant for HD, are rare examined in HD patients (Mason et al., 2021; Snowden, 2017). Evidence on the debut of social cognitive dysfunction have been conflicting, with some studies demonstrating social cognitive dysfunction in the premanifest stage of disease (Eddy et al., 2018; Eddy & Rickards, 2015a, 2015b; Stout et al., 2011), while other studies fail to demonstrate social cognitive dysfunction before the manifest stage of disease (Kipps et al., 2007; Larsen, Vinther-Jensen, Gade, et al., 2016; Milders et al., 2003). A meta-analysis has suggested that social cognitive dysfunction might be more severe in near-onset premanifest individuals, potentially serving as a biomarker for disease progression (Bora et al., 2016). Moreover, it can be speculated that the different functions of social cognition are affected at a different time during the disease. Based on the evidence that emotion recognition abilities have been reported to be associated with volumes of the caudate and putamen, emotion recognition might be an early affected function in HD (Harrington et al., 2014).

Theoretical discussions of the executive elements in social cognitive tests and social cognitive functions make out an integral part. In HD, social cognitive dysfunctions have been linked to executive functions in a number of studies (Brüne et al., 2011; Eddy et al., 2014; Larsen, Vinther-Jensen, Nielsen, et al., 2016), while other studies find social cognitive dysfunction independently from executive dysfunction (Allain et al., 2011; Eddy & Rickards, 2015a). The interesting questions concerns whether the associations between social cognition and executive function are solely explained by the tests used for assessment? Since examinations of social cognition often involve elements that taps executive functions, attention, and retrieval of information, results from such tests are difficult to interpret and the overlap might explain the associations often found between social cognition and executive functions. Another suggestion is that social cognitive abilities draw on executive functions to some degree, explaining why some studies find that the executive dysfunction contributes to the social cognitive impairments in HD. That taking another person's perspective besides one's own requires additional cognitive effort, can demonstrate one explanation for the

involvement of executive functions in social cognition (Bradford et al., 2015). However, the fact that social cognitive dysfunction has been found partially independent from executive dysfunction in HD suggests that social cognition and executive functions are dissociable functions (Allain et al., 2011; Eddy & Rickards, 2015a). This has also been suggested in studies of patients with traumatic brain injury (Aboulafia-Brakha et al., 2011; Havet-Thomassin et al., 2006; Muller et al., 2010).

Finally, the importance of social cognitive abilities in activities of daily functioning is poorly elucidated in HD despite the apparent relevance of the subject. Social cognitive dysfunction affects every social interaction with other people, and the complex capacities involved in social negotiations are specifically important for the functional capacity in HD. Only a few studies examining the association between social cognition and functional capacity have been performed and come to conflicting conclusions (Brüne et al., 2011; Eddy et al., 2014; Ille et al., 2011; Tabrizi et al., 2013). When considering the multiple situations of daily function and social interactions, where social cognitive functions are important, the lack of evidence warrants more thorough investigations.

STUDY III: CHANGES IN THE SELF-PERCEPTION OF AUTONOMY

Changes in self-perception has not previously been examined in HD. As a neurodegenerative disease affecting the motoric and functional abilities, cognitive function, and the psychiatric status of a person with the disease, HD imposes profound life changes on the person with adverse effects on functional independence and mobility, employment prospects, and social life (Craufurd & Snowden, 2014). Consequently, HD might affect the perception of self.

In dementia, research has investigated the consequences of having a neurodegenerative disease on the perception of self (Caddell & Clare, 2010; Strikwerda-Brown et al., 2019). What constitute the self is often very differently conceptualised but overall, the evidence suggests some persistence in the perception of self, while other aspects of self are deteriorated. In Alzheimer's disease, a weakened sense of self and an impaired self-concept have been demonstrated (Addis & Tippett, 2004; Martinelli et al., 2013). In other studies, it has been emphasised that some aspects of identity in patients with Alzheimer's disease persists, even in severe stages of the disease (Cohen-Mansfield et al., 2000; Eustache et al., 2013). Some studies have focused on autobiographical memory, which is thought to facilitate a continuity in the feelings of self and identity, as it helps to integrate past and present selves in the self-narrative (Addis & Tippett, 2004). The investigation of the association between the perception of self and cognitive impairments have shown limited evidence and it is still unclear whether cognitive decline in neurodegenerative diseases might affect the perception of self (Caddell & Clare, 2013).

Since memory functions are often affected by dementia (including autobiographical memory), the changes to self might be more apparent in dementia, than in early stages of HD, where memory impairments might not be as prominent. However, the investigation of changes to self-perception in HD and in other neurodegenerative diseases are still very relevant, as it has a number of important implications. These include patients' ability to cope with their disease, their ability to form and preserve social relationships and interactions with family, friends, and professionals, and it can inform us on the type of intervention relevant for them (Caddell & Clare, 2010, 2013).

The perception of autonomy as an aspect of the self, include the ability to self-regulate motivation and actions (Ryan & Deci, 2000, 2006). The study of autonomy has high clinical relevance for HD, as a low degree of autonomy has been linked to higher risk of depression and anxiety, among other psychopathologies, in the normal population (Bekker & Belt, 2006; Rutten et al., 2016; Ryan et al., 2006, 2016). Thus, if the self-perception of autonomy is affected by HD to some degree, this might help explain why some individuals with HD experience more psychopathology than others. Irrespective, the investigation of autonomy in HD can help demonstrate if the neurodegeneration of HD affects the self-perception of autonomy, and if the dependence on others with the increasing symptoms has a consequence for the perception of self.

Aims

The overall aim of this PhD project was to investigate neuropsychological and behavioural changes in premanifest and motor-manifest Huntington's disease (HD) gene expansion carriers. To accomplish this aim, three studies were conducted to investigate symptoms of apathy, social cognitive dysfunction, and changes in the self-perception of autonomy. A further aim was to conduct follow-up examinations on a large single-site cohort of HD gene expansion carriers and gene-negative family-based controls previously examined in year 2012-2013 (Study II).

Study objectives:

Study I: Characterising apathy in HD

- To examine the presence of apathy in HD using two different instruments
- To investigate which subtypes of apathy were affected in HD gene expansion carriers
- To examine which symptoms of HD could predict the presence of apathy

Study II: Social cognitive dysfunction and functional decline in HD

- To examine if the HD gene expansion carriers who were impaired on the cognitive domains *executive function* and *social cognition* were the same or different
- To investigate which of the cognitive domains could predict the decline in functional capacity over a 6-year follow-up period

Study III: Changes in the self-perception of autonomy

- To explore the self-perception of autonomy in HD gene expansion carriers
- To examine if autonomy was associated with neuropsychiatric symptoms, cognitive status, apathy, or motor function in HD

Methods

This PhD project consisted of a prospective cohort of Huntington's disease (HD) gene expansion carriers and gene-negative family controls which was examined in the clinic in year 2017-2021. The cohort included participants originally enrolled in year 2012-2013, who were followed up with new neurological and neuropsychological examinations, and new participants enrolled in the cohort for the first time. The examinations performed in year 2017-2021 constitute the basis of this PhD project, but results from year 2012-2013 are included in Study II. In the following, the cohort of year 2012-2013 will be referred to as participants from Time 1 and the cohort of year 2017-2021 will be referred to as participants from Time 2.

PARTICIPANTS

The participants from all studies in this project were enrolled from the Neurogenetics Clinic and the Danish Dementia Research Centre at the Neurological Department, at Rigshospitalet – Blegdamsvej in Denmark. Participants from Time 1 have been described previously (Larsen et al., 2015; Vinther-Jensen et al., 2014). The HD gene expansion carriers from Time 1 were contacted and invited to participate in the follow up examinations. New participants were invited to take part in the study for the first time. A total of 88 participants took part in the project at Time 2, with an additional 20 participants from Time 1 not included in the neuropsychological assessment and therefore only included in Study II as follow-up participants. New participants were responders to an advertisement in the newsletter of the Danish Huntington's Disease Association or responders of word-to-mouth invitation (N = 28). A flowchart over inclusion of participants at Time 1 and Time 2 can be seen in figure 2.

New participants were included based on the same criteria applied at Time 1: a cytosine-adenine-guanine (CAG) repeat length ≥ 39, an Unified Huntington's Disease Rating Scale (UHDRS) – Total Motor Score (TMS) < 55 (Huntington's Study Group, 1996), a Montreal Cognitive Assessment (MoCA) score ≥ 19 (Nasreddine et al., 2005), and a Mini-Mental State Examination (MMSE) score ≥ 24 (Folstein et al., 1975). The exclusion criteria were other neurological disease, an ongoing alcohol- or drug abuse, or a native language other than Danish.

Genetical counselling and information on their genetic status were received by all participants prior to and independently from enrolment in the studies of this project.

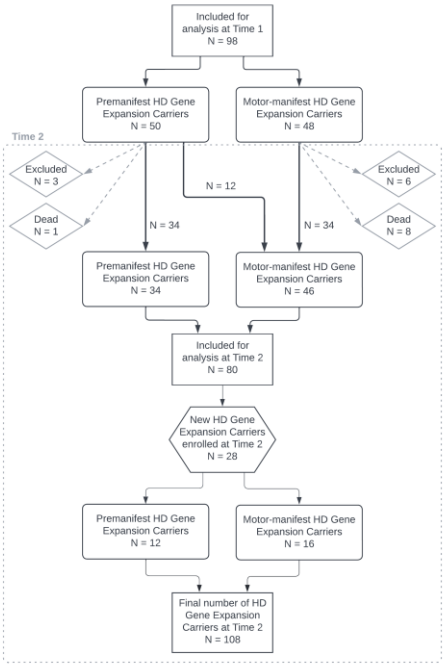

Figure 2. Inclusion of participants at Time 1 and Time 2. The figure is modified from manuscript III, Hendel, Hellem, Larsen, et al. (2022).

Classification of participants

The HD gene expansion carriers were classified as premanifest HD gene expansion carriers if they had an UHDRS-TMS ≤ 5 and presented without substantial motor symptoms that could be explained by HD. A classification of motor-manifest HD gene expansion carriers was applied if the participants scored > 5 on the UHDRS-TMS.

Controls

The control group consisted of family members, at-risk for inheriting the HD gene expansion, but who were tested negative (a CAG repeat length < 30). This family-based control group were chosen over unrelated healthy controls to better match for psychosocial and environmental factors from growing up in a family with HD.

Participants included in studies

The difference in participants included in the studies are explained in the following. Please see table 1 for an overview of the number of participants in the studies.

Study I Participants from Study I included 82 HD gene expansion carriers (40 premanifest HD gene expansion carriers and 42 motor-manifest HD gene expansion carriers). All participants were examined at Time 2 and included both participants who had participated in the project at Time 1 and new participants. In manuscript II, two motor-manifest HD gene expansion carriers were excluded from the study, because of a lack of cognitive data.

The study included 32 control participants, of which both new controls and controls who participated in the cohort at Time 1 were included.

Study II This study solely included participants who had participated in the cohort at Time 1 and who were invited to take part in the cohort again at Time 2. The final number of participants was 98 at Time 1 (50 premanifest and 48 motor-manifest HD gene expansion carriers) and 80 at Time 2 (34 premanifest and 46 motor-manifest HD gene expansion carriers). Twenty HD gene expansion carriers did not take part in the neuropsychological examination at Time 2 but fulfilled the criteria for being included in this study, since neuropsychological data from Time 1 were available.

Table 1. Number of participants included in the studies and manuscripts.

	HD Gene Expansion Carriers		
	Premanifest	Motor-Manifest	Controls
Study I			
Manuscript I	40	42	32
Manuscript II	40	40	32
Study II			
Manuscript III			
Time 1	50	48	46
Time 2	34	46	46
Study III			
Manuscript IV	20	24	19

The control group was a combined control group that consisted of both new participants and participants who had previously taken part in the cohort at Time 1 (N = 46). Scores from the controls were taken from their initial examination, so that scores from Time 2 were only included for new control participants (N = 7). This was decided in order to avoid any practice effects, and to better equalise the scores.

Study III The participants of Study III included participants who had previously taken part in Study I and who were invited to take part in an additional short exploratory study in year 2020-2021. The participants included both new participants and participants who had taken part in the cohort at Time 1. In total, 44 HD gene expansion carriers took part in the study, consisting of 20 premanifest and 24 motor-manifest HD gene expansion carriers.

The control group included 19 controls, who had previously taken part in Study I and included control participants from the cohort examined at Time 1, as well as new control participants from Time 2.

PROCEDURE

This PhD project was approved by the Ethics Committee of the Capital Region of Denmark (H2-2011-085 and H-17002606). We obtained written informed consent from all participants before their enrolment in the project. Two visits were scheduled for all participants and performed in a random order: a neurological examination and a neuropsychological assessment. For the participants of Study III, another neuropsychological assessment (comprising instruments on self-perception) was scheduled about a year after the first one.

Neurological examination

The neurological examination included measures on motor function (UHDRS-TMS) (Huntington's Study Group, 1996), cognitive status (MMSE and the MoCA) (Folstein et al., 1975; Nasreddine et al., 2005), neuropsychiatric illness (the Symptom Checklist revised, SCL-90-R and the Hamilton Depression Scale, HAM-17) (Derogatis, 2009; Hamilton, 1960), and behavioural symptoms (the short Problem Behavior Assessment for Huntington's Disease, PBA-s) (Callaghan et al., 2015). The functional capacity was assessed across the 6-year follow-up period between Time 1 and Time 2 using the UHDRS Total Functional Capacity scale (UHDRS-TFC) (Huntington's Study Group, 1996). The instruments are presented in table 2.

Table 2. Description of instruments and measures included in the neurological examination.

	Description
Neurological Examination	
CAP	A CAG Age Product (CAP) score was calculated for all HD gene expansion carriers as $CAP = Age \cdot (CAG - 35.5)$ based on the formula by Penney et al., (1997).
Motor function	
UHDRS-TMS	The Unified Huntington's Disease Rating Scale – Total Motor Score (UHDRS-TMS) is a standardized rating scale on motor symptoms in HD (Huntington's Study Group, 1996). The UHDRS-TMS include 31 items rated on a 4-point Likert scale, ranging from 0 (normal) to 4

(severe impairment). The UHDRS-TMS yields a total score of 0–124, where a higher score indicates more severe motor disabilities.

Cognitive status

MMSE

The Mini-Mental State Examination (MMSE) is a widely used cognitive screening instrument examining the cognitive status of an individual (Folstein et al., 1975). The MMSE has a high focus on memory abilities, but other cognitive functions are also examined. It yields a total score of 0-30, where a higher score indicates better cognitive performance.

MoCA

The Montreal Cognitive Assessment (MoCA) is another cognitive screening instrument investigating the cognitive status of an individual (Nasreddine et al., 2005). Unlike the MMSE, the MoCA has a greater focus on executive functions which makes it more sensitive to the early changes in HD. The MoCA yields a total score of 0-30, where a higher score indicates better cognitive performance.

Neuropsychiatric illness

HAM-17

The Hamilton Depression Scale (HAM-17) is semi-structured interview examining depression (Hamilton, 1960). The HAM-17 contains 17 items on depressive symptoms, scored on a 5-point Likert scale (0-4) or a 3-point scale (0-2), where a higher score indicates increased severity of the symptoms.

SCL-90-R

The Symptom Checklist – Revised (SCL-90-R) is a self-report scale that examines the psychological status of the subject within the past seven days (Derogatis, 2009). It contains 90 items on psychological symptoms that can lead to distress. The items are answered on a 5-point Likert scale, ranging from 1 (not at all) to 5 (extremely distressing). The SCL-90-R yields nine symptom dimensions and three global indexes: The Global Severity Index, the Positive Symptom Total, and the Positive Symptom Distress Index. In this project, all raw scores were converted to T scores, by normalizing data to a sample of nonpsychiatric danish participants, sorted by gender (Olsen et al., 2004).

Behavioural symptoms

PBA-s

The Short Problem Behavior Assessment for Huntington's Disease (PBA-s) assesses behavioural symptoms in individuals with HD, through a semi-structured interview (Callaghan et al., 2015). The PBA-s has 11 items which are scored on a 5-point Likert scale for both the frequency and severity of the symptom, ranging from 0 (absent) to 4 (present all the time/causing severe problems). Ratings are based on information from the patient, an informant and the clinicians own clinical observations.

Functional Capacity

UHDRS-TFC

The Unified Huntington's Disease Rating Scale – Total Functional Capacity (UHDRS-TFC) is an interview that assesses the functional capacities of individuals with HD (Huntington's Study Group, 1996).

It contains 5 items, covering basic functions of daily life (occupation, handling of finances, domestic responsibilities) and activities of daily living (bathing, dressing, eating, level of care – facility or home). A total score of 0–13 indicates the level of functional capacity, with a higher score indicating better function.

Neuropsychological assessment

For Study I and II, the participants were assessed with a 3-4 hour long neuropsychological test battery. They were encouraged to take breaks during the assessment to avoid exhaustion and fatigue. For some participants the assessment was performed over two days. The battery included tests on premorbid level of intelligence, psychomotor speed and attention, memory, visuospatial functions, executive functions, social cognition, and apathy. The instruments of the neuropsychological assessment relevant for this PhD thesis are presented in the following and described in table 3.

Executive Functions The instruments used to assess executive functions were the Fluency tests (Lezak, Howieson & Loring, 2004), the Symbol Digit Modality test (SDMT) (Smith, 1982), the Brixton test (Burgess & Shallice, 1997), the Stroop test (Stroop, 1935), and the Trail Making test part B (TMT B) (Reitan, 1955).

Social Cognition Instruments of the social cognitive functions were the Emotion Hexagon test (EH) (Calder et al., 1996; Sprengelmeyer et al., 1996), the Reading the mind in the eyes test (RMET) (Baron-Cohen et al., 2001), and the Awareness of Social Inference test (TASIT), Social Inference – Minimal (SI-M) (McDonald et al., 2003).

Classification of Cognitive Impairments In Study II, participants were classified as impaired or not on the two cognitive domains *social cognition* and *executive functions*, using the methods described below.

Based on the cognitive performance scores of the controls from Time 1, we calculated normative regression-based reference data, correcting for age, sex, and educational index score. Percentile estimates were calculated for the expected score, representing the inverse of the normal cumulative distribution function as specified by the regression model. For each test, the observed scores of each participant at Time 1 was compared to the estimated expected score for the relevant group. If the score was at or below the 10^{th} percentile estimate, the participant was classified as impaired on the specific test. We applied a classification of impaired on *social cognition* if the participants were impaired on one or more of the three social cognitive tests. A classification of impaired on *executive functions* was applied if the participants were impaired on two or more of the six included executive tests.

Apathy The assessment of apathy was performed using the PBA-s (Callaghan et al., 2015) and the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006). The two instruments were administered independently, without the knowledge of the scores of the other. Regression-based reference data correcting for age, sex, and educational index score was calculated based on the scores of the controls on the Global LARS. The HD gene expansion carriers with a score $\leq$ 10^{th} percentile of the controls were classified as apathetic. On the PBA-s, we used a cut-off score of ≥ 2 on the Apathy subscale to classify apathetic participants. The Apathy subscale was

based on the product score of the severity score and the frequency score on the Apathy item.

Self-perception

The participants of Study III were examined with a short 1-hour battery on self-perception. The battery contained instruments on self-identity, autonomy, apathy, and neuropsychiatric symptoms. Relevant for this PhD thesis is the scores on measures of autonomy, apathy, and neuropsychiatric illnesses. The instruments on autonomy were the Autonomy-Connectedness Scale (ACS-30) (Bekker & van Assen, 2006) and the Index of Autonomous Functioning (IAF) (Weinstein et al., 2012). Both instruments were translated to Danish and back-translated to English in agreement with the authors of the original scales. A classification of a low degree of autonomy was applied if the motor-manifest HD gene expansion carriers had a degree of autonomy that was lower than or equal to the 10^{th} percentile score of the controls. The instruments are described in table 3.

Table 3. Description of instruments and measures applied in the neuropsychological assessment and the assessment of self-perception.

Neuropsychological Assessment	Description
Executive Functions	
Fluency Tests	The participants were examined with four fluency tests. In the Lexical Fluency test, participants must within one minute name as many words as possible beginning with each of the letters F, A, and S (Lezak, Howieson & Loring, 2004). In the Semantic Fluency test the participants should name as many animals as possible within one minute. Both types and categories of animals were accepted. In the Lexical Alternating Fluency test (K-B words), the participants should name as many words as possible within one minute beginning with the letters K and B, in an alternating order. In the Semantic Lexical Alternating Fluency test (Food-D words) the participants should name as many words as possible alternating between words beginning with the letter D and names of food found in a supermarket. The participants had one minute to name as many as possible. For all the fluency tests, we accepted all Danish words, except for proper nouns.
SDMT	The Symbol Digit Modalities test (SDMT) investigates psychomotor speed, with a brief substitution test where participants use a reference key to pair nine different numbers with specific geometric symbols (Smith, 1982). Participants have 90 sec to pair as many numbers as possible.
The Brixton Test	The Brixton test is a test of task analysis. By using a stimulus book, the participants are presented with ten circles numbered 1-10 in the same basic display, but for each page in the book one circle is printed blue (Burgess & Shallice, 1997). With no feedback, the participants must on each page indicate the position of the blue circle on the next page by guessing the pattern of the movement of the blue circle, based on the positions from previous pages.

The Stroop Test

The Stroop Interference test is a test of interference and inhibition (Stroop, 1935). In the interference test of the 100-word version, participants must name the colour of the ink that the words are printed in as fast as possible. The words are names of colours which does not correspond to the printed ink, for example would the word yellow be printed in green, and the participants should say green.

TMT B

The Trail Making test part B (TMT B) measures set-shifting. Participants must connect circles with the numbers 1-13 and the letters A-L, alternating between numbers and letters in an ascending sequence (Reitan, 1955).

Social Cognition

EH

The Emotion Hexagon (EH) assesses facial emotion recognition (Calder et al., 1996; Sprengelmeyer et al., 1996) using 30 pictures of facial expressions of the six basic emotions (happiness, surprise, fear, sadness, anger, and disgust). Each picture was morphed along a spectrum, so that each emotion was blended with the two neighbouring emotions with a ratio of 90:10, 70:30, 50:50, 30:70, and 10:90. As an example, happiness was blended with surprise and anger. The participants must indicate the emotion with the highest ratio in each picture. Emotions blended by 50 % were neutral stimuli and were not included in the total score.

RMET

The Reading the Mind in the Eyes test (RMET) is a test of theory of mind (Baron-Cohen et al., 2001). By using 36 pictures of the eye-region of males and females, participants must choose the word from four possibilities which best described the emotional state of the portraited person. The pictures depicted various negative and positive emotional states and each picture were presented with four different words of emotional states. The participants were presented with a wordlist where every word was described and used in a sentence.

TASIT

The Awareness of Social Inference test (TASIT), Social Inference – Minimal (SI-M) is a test of sarcasm detection (McDonald et al., 2003). It consists of 15 short, videotaped vignettes of everyday conversations between two persons. The videotaped vignettes are translated to Danish (Bliksted et al., 2014). The vignettes are either portraying sincere conversational exchanges (five vignettes), simple sarcasm, where the words and paralinguistic and facial cues are incongruent (five vignettes), or paradoxical sarcasm, where the dialogue is only meaningful if it is understood that the person is being sarcastic (five vignettes). For each vignette, the participants must answer four questions, that investigates the participant's perception of the conversation.

Apathy

LARS

The Lille Apathy Rating Scale (LARS) is a standardized structured interview on apathy (Sockeel et al., 2006). It contains 33 items, that are divided into 9 different domains, based on the clinical manifestations of apathy. The items are either answered on a 5-point

	Likert Scale, ranging from -2 to 2 (items 1-3), or on a binary yes/no scale (-1 to 1, with an additional 0, for not applicable). The interview yields a global score (-36 to 36) and four subtypes describing the distinct dimensions of apathy: Intellectual Curiosity, Emotions, Action Initiation, and Self-Awareness (-4 to 4). A higher score indicates a higher degree of apathy.
Assessment of Self-Perception	
ACS-30	The Autonomy-Connectedness Scale (ACS-30) is a self-report questionnaire on autonomy with 30 questions, answered on a 5-point Likert scale ranging from 1 (disagree) to 5 (agree) (Bekker & van Assen, 2006). The scale contains three subscales: Sensitivity to Others, Capacity for Managing New Situations, and Self-Awareness. A higher score represents a higher degree of autonomy.
IAF	The Index of Autonomous Functioning (IAF) is a self-report questionnaire on autonomy (Weinstein et al., 2012). It includes 15 questions answered on a 5-point Likert scale, ranging from 1 (not at all true) to 5 (completely true). The IAF consist of three subscales: Authorship/Self-Congruence, Interest-Taking, and Susceptibility to Control. A total score is calculated based on the scores from the subscales as Total IAF = Author + Interest − Control. A higher total score represents a higher degree of autonomy.

Results

This section will cover the main results of Study I-III. The results will be presented in separate subsections for each study. For details on the demographic information of the groups and specific results not presented here, please refer to the manuscripts in appendix.

CHARACTERISING APATHY IN HD (STUDY I)

Characterising of apathy using two different instruments: the Lille Apathy Rating Scale (LARS) and the short Problem Behaviors Assessment (PBA-s) was a main outcome of study I. The results demonstrated that the motor-manifest Huntington's disease (HD) gene expansion carriers had a significantly higher degree of apathy on both the PBA-s Apathy subscale and the Global LARS when compared with the premanifest HD gene expansion carriers and the controls (see table 4). The PBA-s Apathy subscale and the Global LARS was significantly associated, but the effect was medium-sized and indicated that the two instruments only to some extent examined the same construct. The scores of the premanifest HD gene expansion carriers were not significantly different from the scores of the controls on both apathy instruments.

The HD gene expansion carriers were classified as apathetic or nonapathetic based on the criteria described in the method section. When applying the LARS 28% HD gene expansion carriers were classified as apathetic. This corresponded to 16 motor-manifest and 7 premanifest HD gene expansion carriers. When compared with the nonapathetic, the apathetic HD gene expansion carriers had a significantly higher motor score and scores on the neuropsychiatric screening tests. The scores on the cognitive screening tests did not differ statistically between the apathetic and the nonapathetic HD gene expansion carriers.

When the PBA-s Apathy subscale was applied, 16.4% of the HD gene expansion carriers were classified as apathetic. These individuals only included motor-manifest HD gene expansion carriers (N = 12). The results indicate that motor-manifest participants were more frequently classified as apathetic than the premanifest participants, when both the LARS and the PBA-s were applied.

Applying the LARS to identify subtypes of apathy

The results demonstrated that the motor-manifest participants had a higher degree of apathy on the subscales Intellectual Curiosity and Action Initiation when compared to the premanifest participants and the controls (see table 4). The difference between the motor-manifest HD gene expansion carriers and the controls on the Action Initiation subscale had the highest effect (r = - 0.51). When correcting for multiple comparisons, the difference between the motor-manifest and the premanifest HD gene expansion carriers on the Intellectual Curiosity subscale could no longer be considered significant.

Table 4. Scores on the PBA–s Apathy subscale and on the LARS for the HD gene expansion carriers and the controls.

	HD Gene Expansion Carriers		Controls
	Premanifest	Motor-Manifest	
N	40	42	32
PBA–s Apathy subscale score	0.1 (0.2)	1.2 (2.0)†‡	0.1 (0.3)
Global LARS score	–25.2 (4.3)	–21.2 (6.7)†‡	–26.3 (3.0)
Intellectual Curiosity score	–2.8 (0.7)	–2.4 (0.9)†	–2.9 (0.5)
Emotions score	–2.6 (1.0)	–2.3 (1.0)	–2.6 (0.7)
Action Initiation score	–3.4 (0.7)	–2.4 (1.1)†‡	–3.5 (0.6)
Self-Awareness score	–2.1 (1.8)	–2.3 (1.6)	–2.5 (1.5)

Note. †Statistically significant difference from the controls ($p < 0.05$). ‡Statistically significant difference from the individuals with premanifest HD ($p < 0.05$).
HD: Huntington's disease. **LARS:** Lille Apathy Rating Scale. **PBA–s:** The short Problem Behaviors Assessment for Huntington's Disease. The table is adapted from manuscript I, Hendel et al. (2021).

Table 5. Correlations between scores on the LARS and the social cognitive and executive tasks for the total group of HD gene expansion carriers.

Social Cognition	Global LARS Score
TASIT SI-M Total Score	-.14
Sincere Score	-.13
Simple Sarcasm Score	-.02
Paradoxical Sarcasm Score	-.07
EH Total Score	*-.27**
RMET Total Score	-.20
Executive Functions	
SDMT Total Score	*-.33**
TMT B (sec)	*.28**
Lexical Fluency Score	*-.27**
Semantic Fluency Score	*-.35**
Alternating Fluency Score	*-.27**
Stroop Test Incongruence Score (sec)	.19
Brixton Test Score	.19

Note. * Statistically significant ($p < .05$).
HD: Huntington's Disease. **LARS:** The Lille Apathy Rating Scale. **TASIT:** The Awareness of Social Inference test. **SI-M:** Social Inference Minimal. EH: Emotion Hexagon. **RMET:** Reading the Mind in the Eyes test. **SDMT:** Symbol Digit Modality test. **TMT B:** Trail Making test B. The table is adapted from manuscript II, Hendel, Hellem, Hjermind, et al. (2022a).

Predicting the presence of apathy

In the combined group of HD gene expansion carriers, apathy (the LARS score) was significantly associated with the motor function, the cognitive status, and the neuropsychiatric symptoms. In contrast, no significant associations were found between apathy and age, the cytosine-adenine-guanine (CAG) repeat length, or the CAG Age Product (CAP) score. When examining the cognitive measures, we found that apathy was significantly negatively associated with the Emotion Hexagon (EH) score and with most executive tasks (see table 5).

Two regression models were applied to investigate if symptoms of HD could predict the presence of apathy on the Global LARS score. In the first model, it was examined if motor function, cognitive status, or neuropsychiatric illness could explain the presence of apathy. The motor function and depression scores were significant predictors of apathy, while the cognitive status did not contribute significantly (see table 6 – Model 1). This model explained 21% of the total variance. The second model investigated if executive and social cognitive functions had significant impact on the degree of

apathy. The motor function and the depressive symptoms once again were significant predictors of apathy, while the cognitive variables did not contribute significantly to the prediction of apathy (see table 6 – Model 2). The model explained 21% of the total variance and was essentially the same model as model 1.

SOCIAL COGNITIVE DYSFUNCTION AND FUNCTIONAL DECLINE (STUDY II)

The predictive properties of the domains of *social cognition* or *executive functions* for the decline in functional capacity across a follow-up period of 6 years was examined in this study. The study was a follow-up study assessing participants at Time 1 (year 2012-2013) and at Time 2 (year 2017-2021). At Time 1, the motor-manifest participants performed significantly worse than the premanifest participants and the controls on all the social cognitive and executive tasks. The same was found at Time 2. About one third of all HD gene expansion carriers were impaired on each of the social cognitive tasks (for classification please see the Methods section). The performances of half of the HD gene expansion carriers (51%) were classified as impaired on *social cognition*. For the domain *executive functions* more than half of the HD gene expansion carriers were classified as impaired on the domain (55%).

Despite a substantial overlap between the HD gene expansion carriers who were classified as impaired on *social cognition* and *executive functions*, a significant difference was found between the participants who were impaired on *social cognition* and the participants who were impaired on *executive functions* ($Chi^2 = 29.85$, $p < .001$).

Significant correlations were found between most social cognitive and executive tests both at Time 1 and at Time 2 (see table 7). Interestingly, the functional capacity (Unified Huntington's Disease Rating Scale, Total Functional Capacity, UHDRS-TFC score) was not significantly correlated with the social cognitive tests at Time 1 and only the Symbol Digit Modalities test (SDMT) and the Trail Making test B (TMT B) scores were significantly correlated with the functional capacity score at Time 1. At Time 2, the functional capacity score was significantly correlated with the EH score and all performances on the executive tests.

Table 6. Model parameter estimates from the two regression models with the Global LARS score as outcome variable for all HD gene expansion carriers.

	Predictor variables	*b*	Std. Err.	*p*-level	CI	
Model 1*	Constant	-24.56	7.55	.002	-39.60;	-9.52
	UHDRS-TMS	0.12	0.05	.022	0.02;	0.22
	MoCA	-0.06	0.27	.819	-0.59;	0.47
	HAM-17	0.43	0.19	.023	0.06;	0.81
Model 2**	Constant	-26.32	0.94	<.001	-28.19;	-24.45
	UHDRS-TMS	0.14	0.05	.003	0.05;	0.23
	HAM-17	0.41	0.19	.034	0.03;	0.79

Note. * $R^2 = .21$, $p < .001$. ** $R^2 = .21$, $p < .001$.

HAM-17: Hamilton Depression Scale. **HD:** Huntington's disease. **MoCA:** Montreal Cognitive Assessment. **TMS:** Total Motor Score. **UHDRS:** Unified Huntington's Disease Rating Scale.

Table 7. Correlation matrix on the social cognitive and executive tasks and the UHDRS-TFC for the motor-manifest HD gene expansion carriers.

	1.	2.[1]	3.[1]	4.[1]	5.	6.	7.[2]	8.	9.[3]	10.[3]
1. UHDRS-TFC	...	.25	.46*	.18	.61**	-.53*	-.39*	.56*	.46*	.53*
2. RMET score	.06	...	.79**	.63**	.58*	-.57*	-.69**	.47*	.71**	.46*
3. EH score	.06	.47*	...	.54*	.60*	-.58*	-.52*	.47*	.58*	.45*
4. TASIT SI-M score	.01	.49**	.43*	...	.52*	-.59*	-.49*	.56*	.46*	.28
5. SDMT score	.37*	.38*	.56**	.46*	...	-.87**	-.80**	.83**	.74**	.65**
6. TMT B score	-.33*	-.57**	-.56**	-.41*	-.77**	...	.76**	-.75**	-.66**	-.54*
7. Stroop Interference score	-.17	-.40*	-.38*	-.54**	-.72**	.64**	...	-.83**	-.88**	-.55*
8. Lexical Fluency (FAS) score	.19	.47*	.40*	.31*	.47*	-.53**	-.59**	...	.85**	.59*
9. Alternating Fluency (K-B) score	.25	.38*	.24	.07	.42*	-.47*	-.55**	.69**	...	.69**
10. Alternating Fluency (Food-D) score	.20	.22	.30*	.25	.37*	-.31*	-.55**	.56**	.56**	...

Note. Correlations below the dotted line is from Time 1 (N = 48) and correlations above the dotted line is from Time 2 (N = 32). * Statistically significant at the level of $p < .05$. ** Statistically significant at the level of $p < .001$.

[1] Data missing from 5 motor-manifest HD gene expansion carriers at Time 2. [2] Data missing from one motor-manifest HD gene expansion carrier at Time 2. [3] Data missing from three motor-manifest HD gene expansion carriers at Time 2.

EH: Emotional Hexagon. **RMET:** Reading the Minds in the Eyes test. **SDMT:** Symbol Digit Modality test. **SI-M:** Social Inference Minimal. **TASIT:** The Awareness of Social Inference test. **TMT B:** Trail Making test B. **UHDRS-TFC:** Unified Huntington Disease Rating Scale – Total Functional Capacity. The table is adapted from manuscript III, Hendel, Hellem, Larsen, et al. (2022).

Table 8. Model parameter estimates from the multiple stepwise regression models with the ΔTFC as outcome variable for all HD gene expansion carriers.

	Variables in the model	b	Std. Error	R^2 Change	p-level
Model 1*	Constant	0.219	0.269		.417
	UHDRS-TMS	0.075	0.025	.275	.004
	Impairment of *social cognition*	1.075	0.483	.044	.029
Model 2**	Constant	3.864	1.428		.008
	UHDRS-TMS	0.073	0.025	.275	.004
	Emotion Hexagon	-0.181	0.074	.053	.016

Note. * R^2 = .319. ** R^2 = .328.

TFC: Total Functional Capacity. **HD:** Huntington's disease. **TMS:** Total Motor Score. **UHDRS:** Unified Huntington's Disease Rating Scale. The table is adapted from manuscript III, Hendel, Hellem, Larsen, et al. (2022).

Predicting the decline in functional capacity

The difference in functional capacity between Time 1 and Time 2 was calculated with the ΔTFC score. For the premanifest HD gene expansion carriers, the ΔTFC score corresponded to a decrease in functional capacity of 0.1 point on the UHDRS-TFC scale across the 6 years of follow up ($\bar{x}$ = 0.1, SD = 0.5). The functional capacity of the motor-manifest HD gene expansion carriers decreased on average by 2.3 point on the UHDRS-TFC scale across the 6 years of follow-up (ΔTFC: $\bar{x}$ = 2.3, SD = 2.2).

The predictive properties of the two cognitive domains for the decline in functional capacity were examined in a regression model. The ΔTFC score was predicted by the motor function at Time 1 and impairments on *social cognition* with statistically significant probability (see table 8 – Model 1). The model explained 32% of the total variance. When the HD gene expansion carriers were impaired on *social cognition*, their functional capacity was decreased by 1.07 points more at Time 2 than the HD gene expansion carriers not impaired on *social cognition*, assuming an equal motor function. The predictive abilities of the social cognitive tasks for the decline in functional capacity across the follow-up period were investigated in a second model. The motor function score at Time 1 and the EH score at Time 1 could significantly predict the decline in functional capacity (see table 8 – Model 2). The model explained 33% of the total variance and demonstrated that for each lost point on the EH task at Time 1, the UHDRS-TFC had an increased decline by 0.18 points at Time 2 (as calculated by a larger ΔTFC score). The two regression models show that the impairments on *social cognition* have a significant impact on functional capacity, and that the predictive abilities of the social cognitive domain were driven by the emotion recognition on the EH task.

CHANGES IN THE SELF-PERCEPTION OF AUTONOMY (STUDY III)

Study III was an investigation of autonomy and specifically if HD can affect the self-perception of autonomy in HD gene expansion carriers. The motor-manifest HD gene expansion carriers had a significantly lower degree of autonomy on the Autonomy-Connectedness Scale (ACS-30) Capacity subscale when compared to the controls (see table 9). On the Total Index of Autonomous Functioning (IAF) scale, the autonomy of the

motor-manifest HD gene expansion carriers was significantly lower than the premanifest HD gene expansion carriers.

Associations between autonomy and the cardinal features of HD

The motor-manifest HD gene expansion carriers were classified as having a low degree of autonomy if their scores were ≤ 10th percentile cut-off score of the controls. Table 10 shows the number and percentage of the motor-manifest HD gene expansion carriers with a low degree of autonomy when applying the 10th percentile cut-off compared to the stricter 5th percentile cut-off score. On the ACS-30 Sensitivity subscale, 25% of the motor-manifest HD gene expansion carriers had a low degree of autonomy. The motor-manifest HD gene expansion carriers with a low degree of autonomy corresponded to 33% on the ACS-30 Capacity subscale and 38% on the ACS-30 Self-Awareness subscale. On the Total IAF, only 8% were classified with a low degree of autonomy.

No significant associations were found between the autonomy subscales and motor function, cognitive status, neuropsychiatric symptoms, and apathy in the HD gene expansion carriers with a low degree of autonomy. For the entire group of motor-manifest participants a significant correlation was found between the ACS-30 Capacity subscale and the Global LARS score (r = -.65, p = .001). For the other autonomy subscales, no significant correlations were found between autonomy and motor function, cognitive status, or neuropsychiatric illness for the entire group of motor-manifest HD gene expansion carriers.

The Total IAF was significantly associated with the ACS-30 Self-Awareness subscale (r_s = .48, p = .019) for the entire group of motor-manifest HD gene expansion carriers. The Total IAF was not associated with any other subscale of the ACS-30 indicating that the Total IAF and the ACS-30 to some degree measures different aspects of autonomy.

Table 9. Scores on the ACS-30 and the IAF for all HD gene expansion carriers and the controls.

	HD Gene Expansion Carriers		
	Pre-manifest	Motor-Manifest	Controls
N	20	24	19
ACS-30			
Sensitivity	54.9 (8.7)	56.8 (7.5)	57.1 (5.4)
Capacity	21.0 (5.6)	19.4 (5.7)*	23.2 (3.9)
Self-Awareness	27.0 (5.3)	25.1 (5.6)	26.8 (3.1)
IAF			
Total Score	28.3 (3.5)	24.5 (6.5)†	26.5 (4.5)

Note. * Statistically significant difference from the controls ($p < .05$). ‡ Statistically significant difference from the premanifest HD gene expansion carriers ($p < .05$).

ACS-30: Autonomy-Connectedness Scale. **HD:** Huntington's disease. **IAF:** Index of Autonomous Functioning. **N:** Number of participants. The table is adapted from manuscript IV, Hendel, Hellem, Hjermind, et al. (2022b).

Table 10. Frequency of the motor-manifest HD gene expansion carriers classified as below the cut-off when using the 10th and the 5th percentile cut-off scores.

	Cut-off	
	10th percentile	5th percentile
ACS-30		
Sensitivity	6 (25%)	1 (4%)
Capacity	8 (33%)	6 (25%)
Self-Awareness	9 (38%)	8 (33%)
IAF		
Total	2 (8%)	2 (8%)

Note. Frequency is indicated as N (%).

ACS-30: Autonomy-Connectedness Scale. **HD:** Huntington's disease. **IAF:** Index of Autonomous Functioning. **N:** Number of participants. The table is adapted from manuscript IV, Hendel, Hellem, Hjermind, et al. (2022b).

Discussion

In this PhD thesis, changes in self-perception, cognition, and behaviour in Huntington's disease (HD), with a focus on apathy, social cognitive dysfunction, and autonomy have been investigated and described. These changes are thought to be specifically challenging for the families that live with HD, since previous studies have demonstrated that cognitive, behavioural, and apathetic symptoms are frequent and specifically burdensome and distressing for families with HD (Craufurd et al., 2001; Fritz et al., 2018; Paulsen et al., 2017; Ready et al., 2008; van Duijn et al., 2007). There is a substantial body of evidence on the neuropsychological deficits of HD in the literature, but research continues to enhance our understanding of the cognitive and behavioural changes that arise as a consequence of the disease.

CHARACTERISATION OF APATHY IN HD (STUDY I)

The results from Study I illustrated that the degree of apathy is higher in motor-manifest HD gene expansion carriers when compared to both premanifest HD gene expansion carriers and controls. An association with disease progression has also been demonstrated in other studies (Camacho et al., 2018; Thompson et al., 2012; van Duijn et al., 2007). Although the Lille Apathy Rating Scale (LARS) had only been used in one other study of HD at the time when the present study took place (De Paepe et al., 2019), we applied the LARS for the assessment of apathy in HD with the advantage that LARS is a specific measure of apathy that can characterise different subtypes of apathy. Likewise, the characterisation of apathy as a multidimensional syndrome with different subtypes in HD was only applied in the De Paepe et al. (2019) study when the present study was conducted. Since then, a few other studies have sought to examine subtypes of apathy in HD (Atkins et al., 2021, 2022). Study I demonstrated that motor-manifest HD gene expansion carriers had a higher degree of apathy on the subtypes Intellectual Curiosity and Action Initiation, compared with family controls. These subtypes include symptoms of diminished initiation, interest, motivation, social life, and everyday productivity (Sockeel et al., 2006). Longitudinal studies should seek to examine if these symptoms of apathy are a specific characteristic of apathy in HD or if other subtypes of apathy are affected at a more severe stage of HD.

The study illustrated that apathy could be predicted by the motor function and the degree of depressive symptoms. Since only 21% of the total variance was explained by the model, other factors besides motor function and depression must also contribute to the prediction of apathy. When apathy was characterised with the LARS, cognitive functions did not have a significant impact on the degree of apathy. Cognitive functions might have had predictive properties if another measure of apathy had been applied, as cognitive impairments are associated with apathy both in HD (Andrews et al., 2020; Baudic et al., 2006; Reedeker et al., 2011; van Duijn et al., 2010) and other neurodegenerative diseases (Dujardin et al., 2009; Starkstein et al., 2006). Variables serving as proxies for disease burden might not help explain the degree of apathy, as the cytosine-adenine-guanine (CAG) repeat length or the CAG Age Product (CAP) score was not significantly correlated with apathy in this study. Other factors associated with apathy including neuropathological changes should be examined in individuals with HD, as in the study by De Paepe et al. (2019).

The association between the scores of depression and apathy have high theoretical relevance, as these symptoms overlap to some degree in neurodegenerative diseases (Lanctôt et al., 2017). The association between apathy and depression may also be explained by overlapping items on the instruments of assessment. When examining the instruments used in this study (the LARS and the Hamilton Depression Scale, HAM-17), the items appear specific, however. Thus, the association seem to demonstrate a genuine overlap between the symptoms of apathy and depression. Based on the present study, the LARS appears to be a valid and functional instrument for the characterisation of apathy in HD gene expansion carriers. The correlation between the Global LARS and short Problem Behavior Assessment for Huntington's Disease (PBA-s) Apathy subscale was only medium-sized suggesting that the PBA-s is not a sufficient measure for the assessment of apathy in HD. Other instruments (as the LARS) based on the theoretical assumption that apathy is a syndrome must be applied for the assessment of apathy in HD.

SOCIAL COGNITIVE DYSFUNCTION AND FUNCTIONAL DECLINE (STUDY II)

Study II showed that the HD gene expansion carriers who were impaired on the domain *social cognition* were different from HD gene expansion carriers who were impaired on *executive functions*. This result contributes to the current discussion on the executive elements involved in social cognition in individuals with HD (Aboulafia-Brakha et al., 2011; Allain et al., 2011; Brüne et al., 2011; Eddy et al., 2014; Eddy & Rickards, 2015a). In this study, the social cognitive domain encompasses specific abilities not explained by the executive deficits of individuals with HD. The criteria applied for the classification of impairments on the cognitive domains might have affected the results. The difference between the participants who were impaired on *social cognition* and *executive functions* might not have been statistically significant, if impairments on *social cognition* were based on similar criteria as *executive functions*. The result that impairments on *social cognition* and the motor function score can predict the decline in functional capacity across a 6-year follow-up period could also have been affected by these criteria. It is well established that executive dysfunction is early and prevalent in HD (Cavallo et al., 2022; Craufurd & Snowden, 2014; Paulsen et al., 2017; Snowden, 2017).The importance of *executive functions* for functional capacity seems apparent but the importance of these deficits for the prediction of functional decline remains unknown. Results from the present study suggest that social cognitive impairments are a marker of functional decline which is more specific than executive dysfunction. As no other study has sought to examine *social cognition* and *executive functions* on a domain level in HD, this should be validated in other studies.

The predictive properties of the social cognitive domain for the HD gene expansion carriers impaired on *social cognition* corresponded to losing one point more on the Unified Huntington's Disease Rating Scale, Total Functional Capacity (UHDRS-TFC) scale after 6 years when compared to the HD gene expansion carriers not impaired on *social cognition* (assuming an equal motor score). Considering the UHDRS-TFC scale of 0-13 points, losing one point corresponds to some effect on the individual's functional capacity. When the specific social cognitive tasks were included as predictive variables, emotion recognition on the Emotion Hexagon (EH) task showed important predictive ability. An example can illustrate this: When comparing an HD gene expansion carrier with a score at the 10^{th} percentile of the controls on the EH task (e.g., 15 points, corresponding to being impaired on the

EH task for a 50–59-year-old) with an HD gene expansion carrier who had full score on the test (36 points), when both have a Total Motor Score (UHDRS-TMS) of 10, the difference in their ΔTFC score is 3.8 points. This corresponds to a decline in the UHDRS-TFC scale that is almost 4 points larger for the HD gene expansion carrier impaired on the EH task, compared with the HD gene expansion carrier with full score on the task across the 6 years of follow-up. This considerable difference could correspond to a difference between Stage I and Stage II on the Shoulson and Fahn Staging System and a difference between a normal function of daily living and a decreased functional capacity, with a lower level of occupation and a need for assistance in the handling of finances (Ghosh & Tabrizi, 2018). This example helps illustrate the predictive abilities of the EH task for the decline in UHDRS-TFC across the 6 years of follow-up. It should be noted, however, that Model 2 only explained 33% of the total variance, leaving two-thirds of the variance unexplained. Thus, other factor beside the emotion recognition and motor function of the HD gene expansion carriers will have an impact on the UHDRS-TFC over time. Although other cognitive tasks were not entered the model, one could argue that executive dysfunction and other cognitive impairments may also be important for the functional capacity of HD gene expansion carriers. As symptoms of apathy have been linked to a decline in UHDRS-TFC, apathy could also help explain the decline over time (Ross et al., 2014; Tabrizi et al., 2013). Unfortunately, symptoms of apathy were not included in this study.

CHANGES IN THE SELF-PERCEPTION OF AUTONOMY (STUDY III)

Study III showed that motor-manifest HD gene expansion carriers have a lower degree of some types of autonomy. Whether this result is an effect of the neurobiological changes implicated in HD or the psychological changes the follows the disease was not examined directly in this study. While changes in autonomy has not previously been examined in HD or in other neurodegenerative disease, it has been suggested that perceived autonomy is decreased in healthy elderly (Sánchez-García et al., 2019). Leading to a hypothesis that HD might accelerate this decreased perception of autonomy. Changes in self-perception of identity have been found in individuals with dementia (Addis & Tippett, 2004; Caddell & Clare, 2010), suggesting that neurodegenerative processes can affect the self-perception of persons with the disease. The study of changes in self-perception and diminished autonomy is important, since the evidence can imply information on the individual's ability to cope with the disease, to make important life decisions, and to interact with others — all capabilities that can be thought to affect the individual's quality of life (Caddell & Clare, 2010, 2013).

The present study further demonstrated that autonomy can be linked to apathy. More specifically, a low self-regulation in new situations was associated with diminished initiation and motivation. This result is theoretically relevant for the understanding of apathy in HD. Since no other subscale of autonomy were linked to apathy, more classical autonomous behaviours might not be associated with apathy.

A primary limitation of Study III was the low number of participants included. As the study was an exploratory study, we did not include a power analysis. The aim was to explore the possible effects of the neurodegeneration of HD on the perception of autonomy and not to demonstrate a final measure of effect. However, it cannot be ruled out that the low number of participants might have resulted in a lack of difference between the groups on the autonomy scales.

In healthy subjects, a low degree of autonomy has been associated with an increased risk of psychopathology, specifically depression and anxiety (Bekker & Belt, 2006; Bieling & Alden, 2001; Marfoli et al., 2021; Rutten et al., 2016). Since depression and anxiety is prevalent in HD, a low degree of autonomy could help identify individuals with a high risk for developing psychopathology (Paoli et al., 2017). The present study could not demonstrate a statistical association between autonomy and depression or anxiety, but this could result from the small sample.

Finally, unlike the previous studies I and II focusing on objective measures, changes in autonomy with a focus on the HD gene expansion carrier's own perception were examined in Study III. This is a specifically difficult objective since it focuses on a phenomenological experience. However, to truly examine how the changes in HD affects the person, changes should be identified both from the perspectives of the others (family members and caregivers) and the perspective of the HD gene expansion carriers themself. Because of the potential bias that this objective includes, it must once again be emphasised that this study was an exploratory study and that more research on this subject is needed.

IMPAIRED AWARENESS OF DEFICITS (STUDY I-III)

Impaired awareness of deficits in persons with HD is an important discussion point for all three studies in this project. Although studies on impaired awareness is scarce in HD, some studies have found that unawareness of symptoms are frequent in HD and is linked to disease severity, cognitive impairments, emotional symptoms, and functional disabilities (Duff et al., 2010; Hoth et al., 2007; McCusker et al., 2013; McCusker & Loy, 2014; Sitek et al., 2014; Wibawa et al., 2020). Moreover, impaired awareness can lead to increased risk of caregiver distress (McCusker & Loy, 2014; Wibawa et al., 2020).

Study I was based on self-reports (on the LARS), and self-report measures were also used for the investigation of changes in self-perception of autonomy in Study III. As impaired awareness of deficits has been found to exist in about 50% of HD gene expansion carriers, using self-report measures can lead to bias (McCusker et al., 2013). Consequently, the HD gene expansion carriers with impaired awareness might have under-reported on their apathetic symptoms in Study I. In study III, impaired awareness could have affected the number of extreme answers on the self-report measures of autonomy. Although this is a limitation of the present project, some studies have demonstrated that HD gene expansion carriers in the early stages of disease do have insight into their apathetic symptoms (Atkins et al., 2021; Baake et al., 2018; Mason & Barker, 2015).

Study II were not directly affected by impaired awareness, as the social cognitive functions were assessed using quantitative measures. However, the emotion recognition abilities of the cohort at Time 1 were associated with lower psychological distress (Larsen, Vinther-Jensen, Nielsen, et al., 2016). A possible lack of insight into their psychological symptoms combined with affective flattening, that could impair the recognition of emotions. This coincides with studies showing that impaired awareness is associated with lower levels of depression, suggesting that unawareness serves as a psychological coping mechanism for neuropsychiatric symptoms and loss of function in HD (Andrews et al., 2018; Hoth et al., 2007; Sitek et al., 2014).

Conclusions and Future Perspectives

This PhD project demonstrates that changes in the self-perception, cognition, and behaviour can arise in Huntington's disease (HD). Both from specific deficits perceived by others (Study I-II) and changes perceived by the HD gene expansion carriers themself (Study III). The results showed that apathetic symptoms, social cognitive dysfunction, and a low degree of autonomy were more prevalent in the motor-manifest stage of disease compared to the premanifest stage of disease and were not a result of growing up in a family with HD, as family controls were not affected. Hopefully, a more comprehensive description of these deficits will contribute to a better understanding of the cognitive and behavioural symptoms that arise in HD. This could benefit by providing better psychoeducation to family members and caregivers, and in turn reduce the distress that these deficits might lead to.

Study I

- Apathy is frequent in HD and follows the disease progression. Apathy in HD is characterised by symptoms of diminished initiation, interest, motivation, social life, and everyday productivity, and are independent from cognitive impairments.

Study II

- Impaired *social cognition* and motor function can predict functional decline. Social cognition involves separate and specific functions, not explained by executive functions in HD.

Study III

- The self-perception of autonomy can decrease in motor-manifest HD gene expansion carriers. The ability to manage new situations can be linked to apathy.

FUTURE PERSPECTIVES

Based on the results from this project, future studies should seek to investigate the subtypes of apathy affected in HD in a longitudinal study. Such study could contribute with evidence on subtypes affected in HD in more severe stages of disease and thereby demonstrate if the subtypes identified in this project are specific for HD. Replication studies should seek to examine if *social cognition* and *executive functions* as domains affected in HD can be differentiated, and if the self-perception of autonomy can be linked to neuropsychiatric symptoms of HD in a large cohort of HD gene expansion carriers. Finally, studies on impaired awareness in HD should seek to validate a reliable measure of impaired awareness and examine the degree to which unawareness can affect assessments of behavioural and cognitive impairments in HD.

Future neuropsychological and neurological examinations on the large single-site cohort of HD gene expansion carriers which was examined in this project will be conducted by the HD research group at the Neurogenetics Clinic and

the Danish Dementia Research Centre at Rigshospitalet - Blegdamsvej. This cohort is unique due to the thorough and comprehensive characterisation of the participants, including both premanifest and motor-manifest HD gene expansion carriers as well as gene-negative family-based controls. Follow-up examinations will contribute to the characterisation of this cohort, and contribute to the evidence on disease progression, cognitive and behavioural deficits, and endophenotypical drifts in HD.

References

Aboulafia-Brakha, T., Christe, B., Martory, M. D., & Annoni, J. M. (2011). Theory of mind tasks and executive functions: A systematic review of group studies in neurology. *Journal of Neuropsychology*, *5*(1), 39–55. https://doi.org/10.1348/174866410X533660

Addis, D. R., & Tippett, L. J. (2004). Memory of myself: Autobiographical memory and identity in Alzheimer's disease. *Memory*, *12*(1), 56–74. https://doi.org/10.1080/09658210244000423

Allain, P., Havet-Thomassin, V., Verny, C., Gohier, B., Lancelot, C., Besnard, J., Fasotti, L., & Le Gall, D. (2011). Evidence for Deficits on Different Components of Theory of Mind in Huntington's Disease. *Neuropsychology*, *25*(6), 741–751. https://doi.org/10.1037/a0024408

Andrews, S. C., Craufurd, D., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., & Stout, J. C. (2018). Executive impairment is associated with unawareness of neuropsychiatric symptoms in premanifest and early Huntington's disease. *Neuropsychology*, *32*(8), 958–965. https://doi.org/10.1037/neu0000479

Andrews, S. C., Langbehn, D. R., Craufurd, D., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., & Stout, J. C. (2020). Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychological Medicine*, 1–7. https://doi.org/10.1017/S0033291720000094

Atkins, K. J., Andrews, S. C., Chong, T. T. J., & Stout, J. C. (2021). Multidimensional Apathy: The Utility of the Dimensional Apathy Scale in Huntington's Disease. *Movement Disorders Clinical Practice*, *8*(3), 361–370. https://doi.org/10.1002/mdc3.13147

Atkins, K. J., Friel, C. P., Andrews, S. C., Chong, T. T. J., Stout, J. C., & Quinn, L. (2022). A qualitative examination of apathy and physical activity in Huntington's and Parkinson's disease. *Neurodegenerative Disease Management*, *12*(3), 129–139. https://doi.org/10.2217/nmt-2021-0047

Aylward, E. H., Nopoulos, P. C., Ross, C. A., Langbehn, D. R., Pierson, R. K., Mills, J. A., Johnson, H. J., Magnotta, V. A., Juhl, A., & Paulsen, J. S. (2011). Longitudinal change in regional brain volumes in prodromal Huntington disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *82*(4), 405–410. https://doi.org/10.1016/B978-0-12-801942-9.00008-2

Baake, V., van Duijn, E., & Roos, R. A. (2018). Huntington's disease gene expansion carriers are aware of their degree of apathy. *Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 183–187. https://doi.org/10.1176/appi.neuropsych.18020031

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *42*(2), 241–251. https://doi.org/10.1017/S0021963001006643

Baudic, S., Maison, P., Dolbeau, G., Boissé, M. F., Bartolomeo, P., Barba, G. D., Traykov, L., & Bachoud-Levi, A. C. (2006). Cognitive impairment related to apathy in early Huntington's disease. *Dementia and Geriatric Cognitive Disorders*, *21*(5–6), 316–321. https://doi.org/10.1159/000091523

Bekker, M. H. J., & Belt, U. (2006). The role of autonomy-connectedness in depression and anxiety. *Depression and Anxiety*, *23*, 274–280. https://doi.org/10.1002/da

Bekker, M. H. J., & van Assen, M. A. L. M. (2006). A Short Form of the Autonomy Scale: Properties of the Autonomy–Connectedness Scale (ACS–30). *Journal of Personality Assessment*, *86*(1), 51–60. https://doi.org/10.1207/s15327752jpa8601

Bieling, P. J., & Alden, L. E. (2001). Sociotropy, autonomy, and the interpersonal model of depression: An integration. *Cognitive Therapy and Research*, *25*(2), 167–184. https://doi.org/10.1023/A:1026491108540

Bliksted, V., Fagerlund, B., Weed, E., Frith, C., & Videbech, P. (2014). Social cognition and neurocognitive deficits in first-episode schizophrenia. *Schizophrenia Research*, *153*(1–3), 9–17. https://doi.org/10.1016/j.schres.2014.01.010

Bonner-Jackson, A., Long, J. D., Westervelt, H., Tremont, G., Aylward, E., & Paulsen, J. S. (2013). Cognitive reserve and brain reserve in prodromal Huntington's disease. *Journal of the International Neuropsychological Society*, *19*(7), 739–750. https://doi.org/10.1017/S1355617713000507

Bora, E., Velakoulis, D., & Walterfang, M. (2016). Social cognition in Huntington's disease: A meta-analysis. *Behavioural Brain Research*, *297*, 131–140. https://doi.org/10.1016/j.bbr.2015.10.001

Bradford, E. E. F., Jentzsch, I., & Gomez, J. C. (2015). From self to social cognition: Theory of Mind mechanisms and their relation to Executive Functioning. *Cognition*, *138*, 21–34. https://doi.org/10.1016/j.cognition.2015.02.001

Brüne, M., Blank, K., Witthaus, H., & Saft, C. (2011). "Theory of mind" is impaired in Huntington's disease. *Movement Disorders*, *26*(4), 671–678. https://doi.org/10.1002/mds.23494

Bunner, K. D., & Rebec, G. V. (2016). Corticostriatal dysfunction in Huntington's disease: The basics. *Frontiers in Human Neuroscience*, *10*(June), 1–12. https://doi.org/10.3389/fnhum.2016.00317

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton tests*. Pearson Assessment.

Caddell, L. S., & Clare, L. (2010). The impact of dementia on self and identity: A systematic review. *Clinical Psychology Review*, *30*(1), 113–126. https://doi.org/10.1016/j.cpr.2009.10.003

Caddell, L. S., & Clare, L. (2013). How does identity relate to cognition and functional abilities in early-stage dementia? *Aging, Neuropsychology, and Cognition*, *20*(1), 1–21. https://doi.org/10.1080/13825585.2012.656575

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial Emotion Recognition after Bilateral Amygdala Damage: Differentially Severe Impairment of Fear. *Cognitive Neuropsychology*, *13*(5), 699–745. https://doi.org/10.1080/026432996381890

Callaghan, J., Stopford, C., Arran, N., Boissé, M. F., Coleman, A., Santos, R. D., Dumas, E. M., Hart, E. P., Justo, D., Owen, G., Read, J., Say, M. J., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., Bachoud-Levi, A. C., Bourdet, C., Van Duijn, E., & Craufurd, D. (2015). Reliability and factor structure of the short problem behaviors assessment for huntington's disease (PBA-s) in the TRACK-HD and REGISTRY studies. *Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(1), 59–64. https://doi.org/10.1176/appi.neuropsych.13070169

Camacho, M., Barker, R. A., & Mason, S. L. (2018). Apathy in Huntington's Disease: A Review of the Current Conceptualization. *Journal of Alzheimer's Disease & Parkinsonism*, *08*(02), 1–9. https://doi.org/10.4172/2161-0460.1000431

Cavallo, M., Sergi, A., & Pagani, M. (2022). Cognitive and social cognition deficits in Huntington's disease differ between the prodromal and the manifest stages of the condition: A scoping review of recent evidence. *British Journal of Clinical Psychology*, *61*(2), 214–241. https://doi.org/10.1111/bjc.12337

Chandra, A., Johri, A., & Beal, M. F. (2014). Prospects for neuroprotective therapies in prodromal Huntington's disease. *Movement Disorders*, *29*(3), 285–293. https://doi.org/10.1002/mds.25835

Cohen-Mansfield, J., Golander, H., & Arnheim, G. (2000). Self-identity in older persons suffering from dementia: Preliminary results. *Social Science and Medicine*, *51*(3), 381–394.

https://doi.org/10.1016/S0277-9536(99)00471-2

Craufurd, D., & Snowden, J. S. (2014). Neuropsychiatry and Neuropsychology. In G. Bates, S. Tabrizi, & L. Jones (Eds.), *Huntington's Disease* (4th ed., pp. 36–65). Oxford University Press.

Craufurd, D., Thompson, J. C., & Snowden, J. S. (2001). Behavioral Changes in Huntington Disease. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, *14*(4), 219–226. https://doi.org/10.1097/WNN.0000000000000147

De Paepe, A. E., Sierpowska, J., Garcia-Gorro, C., Martinez-Horta, S., Perez-Perez, J., Kulisevsky, J., Rodriguez-Dechicha, N., Vaquer, I., Subira, S., Calopa, M., Muñoz, E., Santacruz, P., Ruiz-Idiago, J., Mareca, C., de Diego-Balaguer, R., & Camara, E. (2019). White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. *NeuroImage: Clinical*, *24*(July), 101965. https://doi.org/10.1016/j.nicl.2019.101965

Derogatis, L. R. (2009). *SCL-90-R, Vejledning til administration og scoring, Dansk Version* (L. R. Derogatis (ed.)). Pearson.

Duff, K., Paulsen, J., Mills, J., Beglinger, L. J., Moser, D. J., Smith, M. M., Langbehn, D. R., Stout, J., Queller, S., & Harrington, D. L. (2010). Mild cognitive impairment in prediagnosed Huntington disease. *Neurology*, *75*(6), 500–507. https://doi.org/10.1212/WNL.0b013e3181eccfa2

Dujardin, K., Sockeel, P., Delliaux, M., Destée, A., & Defebvre, L. (2009). Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disorders*, *24*(16), 2391–2397. https://doi.org/10.1002/mds.22843

Eddy, C. M., & Rickards, H. E. (2015a). Interaction without intent: The shape of the social world in Huntington's disease. *Social Cognitive and Affective Neuroscience*, *10*(9), 1228–1235. https://doi.org/10.1093/scan/nsv012

Eddy, C. M., & Rickards, H. E. (2015b). Theory of Mind Can Be Impaired Prior to Motor Onset in Huntington's Disease. *Neuropsychology*, *29*(5), 792–798. https://doi.org/10.1037/neu0000190

Eddy, C. M., Rickards, H. E., & Hansen, P. C. (2018). Through your eyes or mine? The neural correlates of mental state recognition in Huntington's disease. *Human Brain Mapping*, *39*(3), 1354–1366. https://doi.org/10.1002/hbm.23923

Eddy, C. M., Sira Mahalingappa, S., & Rickards, H. E. (2014). Putting things into perspective: the nature and impact of theory of mind impairment in Huntington's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(8), 697–705. https://doi.org/10.1007/s00406-014-0498-4

Epping, E. A., Kim, J. I., Craufurd, D., Brashers-Krug, T. M., Anderson, K. E., McCusker, E. A., Luther, J., Long, J. D., & Paulsen, J. S. (2016). Longitudinal psychiatric symptoms in prodromal Huntington's disease: A decade of data. *American Journal of Psychiatry*, *173*(2), 187–192. https://doi.org/10.1176/appi.ajp.2015.14121551

Eustache, M. L., Laisney, M., Juskenaite, A., Letortu, O., Platel, H., Eustache, F., & Desgranges, B. (2013). Sense of identity in advanced Alzheimer's dementia: A cognitive dissociation between sameness and selfhood? *Consciousness and Cognition*, *22*(4), 1456–1467. https://doi.org/10.1016/j.concog.2013.09.009

Evans, S. J. W., Douglas, I., Rawlins, M. D., Wexler, N. S., Tabrizi, S. J., & Smeeth, L. (2013). Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *Journal of Neurology, Neurosurgery and Psychiatry*, *84*(10), 1156–1160. https://doi.org/10.1136/jnnp-2012-304636

Fahed, M., & Steffens, D. C. (2021). Apathy: Neurobiology, assessment and treatment. *Clinical*

Psychopharmacology and Neuroscience, *19*(2), 181–189. https://doi.org/10.9758/cpn.2021.19.2.181

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State" A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, *12*, 189–198. https://doi.org/10.3744/snak.2003.40.2.021

Fritz, N. E., Boileau, N. R., Stout, J. C., Ready, R., Perlmutter, J. S., Paulsen, J. S., Quaid, K., Barton, S., McCormack, M. K., Perlman, S. L., & Carlozzi, N. E. (2018). Relationships among apathy, health-related quality of life, and function in huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 194–201. https://doi.org/10.1176/appi.neuropsych.17080173

Ghosh, R., & Tabrizi, S. J. (2018). Huntington disease. In *Handbook of Clinical Neurology* (Vol. 147, Issue 3, pp. 255–278). https://doi.org/10.1007/s11825-018-0190-6

Gilling, M., Budtz-Jørgensen, E., Boonen, S. E., Lildballe, D., Bojesen, A., Hertz, J. M., & Sørensen, S. A. (2017). The Danish HD Registry—a nationwide family registry of HD families in Denmark. *Clinical Genetics*, *92*(3), 338–341. https://doi.org/10.1111/cge.12984

Gusella, J. F., Macdonald, M. E., & Lee, J. M. (2014). Genetic modifiers of Huntington's disease. *Movement Disorders*, *29*(11), 1359–1365. https://doi.org/10.1002/mds.26001

Hamilton, M. (1960). A Rating Scale for Depression. *Journal of Neurology, Neurosurgery and Psychiatry*, *23*, 56–62. https://doi.org/10.1192/bjp.bp.107.040485

Harrington, D. L., Liu, D., Smith, M. M., Mills, J. A., Long, J. D., Aylward, E. H., & Paulsen, J. S. (2014). Neuroanatomical correlates of cognitive functioning in prodromal Huntington disease. *Brain and Behavior*, *4*(1), 29–40. https://doi.org/10.1002/brb3.185

Havet-Thomassin, V., Allain, P., Etcharry-Bouyx, F., & Le Gall, D. (2006). What about theory of mind after severe brain injury? *Brain Injury*, *20*(1), 83–91. https://doi.org/10.1080/02699050500340655

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers. *Cognitive and Behavioral Neurology*, *34*(4), 295–302. https://doi.org/10.1097/WNN.0000000000000286

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2022a). On the association between apathy and deficits of social cognition and executive functions in huntington's disease. *Journal of the International Neuropsychological Society*, 1–8. https://jnnp.bmj.com/lookup/doi/10.1136/jnnp-2021-EHDN.64

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2022b). An Exploratory Study Investigating Autonomy in Huntington's Disease Gene Expansion Carriers. *Journal of Huntington's Disease*, 1–9. https://doi.org/10.3233/JHD-220540

Hendel, R. K., Hellem, M. N. N., Larsen, I. U., Vinther-Jensen, T., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2022). Impairments of social cognition significantly predict the progression of functional decline in Huntington's disease: A 6-year follow-up study. *Applied Neuropsychology: Adult*, *0*(0), 1–10. https://doi.org/10.1080/23279095.2022.2073824

Hoth, K. F., Paulsen, J. S., Moser, D. J., Tranel, D., Clark, L. A., & Bechara, A. (2007). Patients with Huntington's disease have impaired awareness of cognitive, emotional, and functional abilities. *Journal of Clinical and Experimental Neuropsychology*, *29*(4), 365–376. https://doi.org/10.1080/13803390600718958

Huntington's Study Group. (1996). Unified Huntington's Disease Rating Scale: reliability and consistency. *Movement Disorders*, *11*(2), 136–142.

Ille, R., Holl, A. K., Kapfhammer, H. P., Reisinger, K., Schäfer, A., & Schienle, A. (2011). Emotion recognition and experience in Huntington's disease: Is there a differential impairment? *Psychiatry Research*, *188*(3), 377–382. https://doi.org/10.1016/j.psychres.2011.04.007

Jacobs, M., Hart, E. P., van Zwet, E. W., Bentivoglio, A. R., Burgunder, J. M., Craufurd, D., Reilmann, R., Saft, C., Roos, R. A., & The REGISTRY investigators of the European Huntington's Disease Network. (2016). Progression of motor subtypes in Huntington's disease: a 6-year follow-up study. *Journal of Neurology*, *263*(10), 2080–2085. https://doi.org/10.1007/s00415-016-8233-x

Kipps, C. M., Duggins, A. J., McCusker, E. A., & Calder, A. J. (2007). Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical Huntington's disease. *Journal of Cognitive Neuroscience*, *19*(7), 1206–1217. https://doi.org/10.1162/jocn.2007.19.7.1206

Lanctôt, K. L., Agüera-Ortiz, L., Brodaty, H., Francis, P. T., Geda, Y. E., Ismail, Z., Marshall, G. A., Mortby, M. E., Onyike, C. U., Padala, P. R., Politis, A. M., Rosenberg, P. B., Siegel, E., Sultzer, D. L., & Abraham, E. H. (2017). Apathy associated with neurocognitive disorders: Recent progress and future directions. *Alzheimer's and Dementia*, *13*(1), 84–100. https://doi.org/10.1016/j.jalz.2016.05.008

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2015). Assessing impairment of executive function and psychomotor speed in premanifest and manifest huntington's disease gene-expansion carriers. *Journal of the International Neuropsychological Society*, *21*(3), 193–202. https://doi.org/10.1017/S1355617715000090

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2016). Do i misconstrue? Sarcasm detection, emotion recognition, and theory of mind in huntington disease. *Neuropsychology*, *30*(2), 181–189. https://doi.org/10.1037/neu0000224

Larsen, I. U., Vinther-Jensen, T., Nielsen, J. E., Gade, A., & Vogel, A. (2016). Social cognition, executive functions and self-report of psychological distress in huntington's disease. *PLoS Currents*, *8*(Huntington Disease), 1–20. https://doi.org/10.1016/j.jalz.2017.06.501

Le Heron, C., Holroyd, C. B., Salamone, J., & Husain, M. (2019). Brain mechanisms underlying apathy. *Journal of Neurology, Neurosurgery and Psychiatry*, *90*(3), 302–312. https://doi.org/10.1136/jnnp-2018-318265

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*, *16*(7), 916–928. https://doi.org/10.1093/cercor/bhj043

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). Verbal Functions and Language Skills. In M. D. Lezak, D. B. Howieson, & D. W. Loring (Eds.), *Neuropsychological Assessment* (4th ed., pp. 501–530). Oxford University Press.

Manera, V., Fabre, R., Stella, F., Loureiro, J. C., Agüera-Ortiz, L., López-Álvarez, J., Hanon, C., Hoertel, N., Aalten, P., Ramakers, I., Zeghari, R., & Robert, P. (2019). A survey on the prevalence of apathy in elderly people referred to specialized memory centers. *International Journal of Geriatric Psychiatry*, *34*(10), 1369–1377. https://doi.org/10.1002/gps.5125

Marfoli, A., Viglia, F., Di Consiglio, M., Merola, S., Sdoia, S., & Couyoumdjian, A. (2021). Anaclitic-sociotropic and introjective-autonomic personality dimensions and depressive symptoms: a systematic review. *Annals of General Psychiatry*, *20*(1), 1–30. https://doi.org/10.1186/s12991-021-00373-z

Martinelli, P., Anssens, A., Sperduti, M., & Piolino, P. (2013). The Influence of Normal Aging and Alzheimer's Disease in Autobiographical Memory Highly Related to the Self. *Neuropsychology*, *27*(1), 69–78. https://doi.org/10.1037/a0030453

Martínez-Horta, S., Perez-Perez, J., Sampedro, F., Pagonabarraga, J., Horta-Barba, A., Carceller-Sindreu, M., Gomez-Anson, B., Lozano-Martinez, G. A., Lopez-Mora, D. A., Camacho, V., Fernández-León, A., Carrió, I., & Kulisevsky, J. (2018). Structural and metabolic brain correlates of apathy in Huntington's disease. *Movement Disorders*, *33*(7), 1151–1159. https://doi.org/10.1002/mds.27395

Mason, S. L., & Barker, R. A. (2015). Rating apathy in Huntington's Disease: Patients and companions agree. *Journal of Huntington's Disease*, *4*, 49–59. http://www.tjyybjb.ac.cn/CN/article/downloadArticleFile.do?attachType=PDF&id=9987

Mason, S. L., Schaepers, M., & Barker, R. A. (2021). Problems with social cognition and decision-making in huntington's disease: Why is it important? *Brain Sciences*, *11*(7). https://doi.org/10.3390/brainsci11070838

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: a clinical review. *European Journal of Neurology*, *25*(1), 24–34. https://doi.org/10.1111/ene.13413

McCusker, E. A., Gunn, D. G., Epping, E. A., Loy, C. T., Radford, K., Griffith, J., Mills, J. A., Long, J. D., & Paulsen, J. S. (2013). Unawareness of motor phenoconversion in Huntington disease. *Neurology*, *81*(13), 1141–1147. https://doi.org/10.1212/WNL.0b013e3182a55f05

McCusker, E. A., & Loy, C. T. (2014). The many facets of unawareness in Huntington disease. *Tremor and Other Hyperkinetic Movements*, *2014*(1), 1–8. https://doi.org/10.7916/D8FJ2FD3

McDonald, S., Flanagan, S., Rollins, J., & Kinch, J. (2003). A new clinical tool for assessing social perception after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *18*(3), 219–238.

Mehrabi, N. F., Singh-Bains, M. K., Waldvogel, H. J., & Faull, R. L. (2016). Cortico-Basal Ganglia Interactions in Huntington's Disease. *Annals of Neurodegenerative Disorders*, *1*(2), 1007. https://pdfs.semanticscholar.org/e807/77d94b0c51340072c6a69be4f5730a184fd8.pdf

Milders, M., Crawford, J. R., Lamb, A., & Simpson, S. A. (2003). Differential deficits in expression recognition in gene-carriers and patients with Huntington's disease. *Neuropsychologia*, *41*(11), 1484–1492. https://doi.org/10.1016/S0028-3932(03)00079-4

Muller, F., Simion, A., Reviriego, E., Galera, C., Mazaux, J. M., Barat, M., & Joseph, P. A. (2010). Exploring theory of mind after severe traumatic brain injury. *Cortex*, *46*(9), 1088–1099. https://doi.org/10.1016/j.cortex.2009.08.014

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment (MoCA): A Brief Screening Tool For Mild Cognitive Impairment. *Journal of American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221

Nobis, L., & Husain, M. (2018). Apathy in Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *22*(Figure 1), 7–13. https://doi.org/10.1016/j.cobeha.2017.12.007

Olsen, L. R., Mortensen, E. L., & Bech, P. (2004). The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. *Acta Psychiatrica Scandinavica*, *110*(3), 225–229. https://doi.org/10.1111/j.1600-0447.2004.00399.x

Pagonabarraga, J., Kulisevsky, J., Strafella, A. P., & Krack, P. (2015). Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment. *The Lancet Neurology*, *14*(5), 518–531. https://doi.org/10.1016/S1474-4422(15)00019-8

Paoli, R. A., Botturi, A., Ciammola, A., Silani, V., Prunas, C., Lucchiari, C., Zugno, E., & Caletti, E. (2017). Neuropsychiatric burden in huntington's disease. *Brain Sciences*, *7*(6), 1–15.

https://doi.org/10.3390/brainsci7060067

Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., Guttman, M., Johnson, S., MacDonald, M., Beglinger, L. J., Duff, K., Kayson, E., Biglan, K., Shoulson, I., Oakes, D., & Hayden, M. (2008). Detection of Huntington's disease decades before diagnosis: The Predict-HD study. *Journal of Neurology, Neurosurgery and Psychiatry*, *79*(8), 874–880. https://doi.org/10.1136/jnnp.2007.128728

Paulsen, J. S., Long, J. D., Johnson, H. J., Aylward, E. H., Ross, C. A., Williams, J. K., Nance, M. A., Erwin, C. J., Westervelt, H. J., Harrington, D. L., Bockholt, H. J., Zhang, Y., McCusker, E. A., Chiu, E. M., Panegyres, P. K., Cross, S., Ryan, P., Epping, E. A., Preston, J., ... Dubinsky, R. (2014). Clinical and biomarker changes in premanifest Huntington disease show trial feasibility: A decade of the PREDICT-HD study. *Frontiers in Aging Neuroscience*, *6*(APR). https://doi.org/10.3389/fnagi.2014.00078

Paulsen, J. S., Miller, A. C., Hayes, T., & Shaw, E. (2017). Cognitive and behavioral changes in Huntington disease before diagnosis. In *Handbook of Clinical Neurology* (1st ed., Vol. 144, pp. 69–91). Elsevier B.V. https://doi.org/10.1016/B978-0-12-801893-4.00006-7

Paulsen, J. S., Ready, R. E., Hamilton, J. M., Mega, M. S., & Cummings, J. L. (2001). Neuropsychiatric aspects of Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *71*, 310–314.

Paulsen, J. S., Smith, M. M., & Long, J. D. (2013). Cognitive decline in prodromal Huntington disease: Implications for clinical trials. *Journal of Neurology, Neurosurgery and Psychiatry*, *84*(11), 1233–1239. https://doi.org/10.1136/jnnp-2013-305114

Penney, J. B., Vonsattel, J.-P., MacDonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG Repeat Number Governs the Development Rate of Pathology in Huntington's Disease. *Annals of Neurology*, *41*, 689–692.

Radakovic, R., & Abrahams, S. (2018). Multidimensional apathy: evidence from neurodegenerative disease. *Current Opinion in Behavioral Sciences*, *22*, 42–49. https://doi.org/10.1016/j.cobeha.2017.12.022

Rawlins, M. D. (2010). Huntington's disease out of the closet? *The Lancet*, *376*(9750), 1372–1373. https://doi.org/10.1016/S0140-6736(10)60974-9

Ready, R. E., Mathews, M., Leserman, A., & Paulsen, J. S. (2008). Patient and Caregiver Quality of Life in Huntington's Disease. *Movement Disorders*, *23*(5), 721–726. https://doi.org/10.1002/mds.21920.Patient

Reedeker, N., Bouwens, J. A., van Duijn, E., Giltay, E. J., Roos, R. A., & van der Mast, R. C. (2011). Incidence, Course, and Predictors of Apathy in Huntington's Disease: A Two-Year Prospective Study. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*, 434–441. https://doi.org/10.1176/appi.neuropsych.23.4.434

Reitan, R. M. (1955). The relation of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology*, *19*(5), 393–394. https://doi.org/10.1037/h0044509

Robert, P., Lanctôt, K. L., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., Hanon, C., David, R., Dubois, B., Dujardin, K., Husain, M., König, A., Levy, R., Mantua, V., Meulien, D., Miller, D., Moebius, H. J., Rasmussen, J., Robert, G., ... Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, *54*, 71–76. https://doi.org/10.1016/j.eurpsy.2018.07.008

Roos, R. A. (2010). Clinical Review Huntington ' s disease. *Orphanet Journal of Rare Diseases*, *5*(40), 1–8.

Roos, R. A. (2014). Clinical Neurology. In G. Bates, S. Tabrizi, & L. Jones (Eds.), *Huntington's Disease* (4th

ed., pp. 25–35). Oxford University Press.

Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology*, *10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24

Rubinsztein, D. C., Leggo, J., Coles, R., Almqvist, E., Biancalana, V. V., Cassiman, J. J., Chotai, K., Connarty, M., Craufurd, D., Curtis, A., Curtis, D., Davidson, M. J., Differ, A. M., Dode, C., Dodge, A., Frontali, M., Ranen, N. G., Stine, O. C., & Sherr, M. (1996). Phenotypic characterization of individuals with 30-40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36-39 repeats. *American Journal of Human Genetics*, *59*(1), 16–22.

Rutten, E. A. P., Bachrach, N., van Balkom, A. J. L. M., Braeken, J., Ouwens, M. A., & Bekker, M. H. J. (2016). Anxiety, depression and autonomy–connectedness: The mediating role of alexithymia and assertiveness. *Psychology and Psychotherapy: Theory, Research and Practice*, *89*(4), 385–401. https://doi.org/10.1111/papt.12083

Ryan, R. M., & Deci, E. L. (2000). Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. *American Psychologist*, *55*(1), 68–78.

Ryan, R. M., & Deci, E. L. (2006). Self-regulation and the problem of human autonomy: Does psychology need choice, self-determination, and will? *Journal of Personality*, *74*(6), 1557–1586. https://doi.org/10.1111/j.1467-6494.2006.00420.x

Ryan, R. M., Deci, E. L., Grolnick, W. S., & La Guardia, J. G. (2006). The Significance of Autonomy and Autonomy Support in Psychological Development and Psychopathology. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental Psychopathology: Volume One: Theory and Method* (pp. 795–849). John Wiley & Sons, Inc.

Ryan, R. M., Deci, E. L., & Vansteenkiste, M. (2016). Autonomy and Autonomy Disturbances in Self-Development and Psychopathology: Research on Motivation, Attachment, and Clinical Process. *Developmental Psychopathology*, *I*, 1–54. https://doi.org/10.1002/9781119125556.devpsy109

Sánchez-García, S., García-Peña, C., Ramírez-García, E., Moreno-Tamayo, K., & Cantú-Quintanilla, G. R. (2019). Decreased autonomy in community-dwelling older adults. *Clinical Interventions in Aging*, *14*, 2041–2053. https://doi.org/10.2147/CIA.S225479

Scahill, R. I., Andre, R., Tabrizi, S. J., & Aylward, E. H. (2017). Structural imaging in premanifest and manifest Huntington disease. In *Handbook of Clinical Neurology* (1st ed., Vol. 144, pp. 247–261). Elsevier B.V. https://doi.org/10.1016/B978-0-12-801893-4.00020-1

Sellers, J., Ridner, S. H., & Claassen, D. O. (2020). A systematic review of neuropsychiatric symptoms and functional capacity in huntington's disease. In *Journal of Neuropsychiatry and Clinical Neurosciences* (Vol. 32, Issue 2, pp. 109–124). American Psychiatric Association. https://doi.org/10.1176/appi.neuropsych.18120319

Sitek, E. J., Thompson, J. C., Craufurd, D., & Snowden, J. S. (2014). Unawareness of deficits in Huntington's disease. *Journal of Huntington's Disease*, *3*(2), 125–135. https://doi.org/10.3233/JHD-140109

Smith, A. (1982). *Symbol Digit Modalities Test: Manual*. Los Angeles: Western Psychological Services.

Snowden, J. S. (2017). The Neuropsychology of Huntington's Disease. *Archives of Clinical Neuropsychology*, *32*(7). https://doi.org/10.1093/arclin/acx086

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(5), 579–584. https://doi.org/10.1136/jnnp.2005.075929

Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H., Hömberg, V., Perrett, D. I., & Rowland, D. (1996). Loss of disgust: Perception of faces and emotions in Huntington's disease. *Brain*, *119*(5), 1647–1665. https://doi.org/10.1093/brain/119.5.1647

Starkstein, S. E., Jorge, R., & Mizrahi, R. (2006). The prevalence, clinical correlates and treatment of apathy in Alzheimer's disease. *European Journal of Psychiatry*, *20*(2), 96–106. https://doi.org/10.4321/S0213-61632006000200005

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive Signs in Prodromal Huntington Disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Strikwerda-Brown, C., Grilli, M. D., Andrews-Hanna, J., & Irish, M. (2019). "All is not lost"—Rethinking the nature of memory and the self in dementia. *Ageing Research Reviews*, *54*(January), 100932. https://doi.org/10.1016/j.arr.2019.100932

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., & Stout, J. C. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *The Lancet Neurology*, *8*(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Reilmann, R., Roos, R. A., Durr, A., Leavitt, B., Owen, G., Jones, R., Johnson, H., Craufurd, D., Hicks, S. L., Kennard, C., Landwehrmeyer, B., Stout, J. C., Borowsky, B., Scahill, R. I., Frost, C., & Langbehn, D. R. (2012). Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: Analysis of 24 month observational data. *The Lancet Neurology*, *11*(1), 42–53. https://doi.org/10.1016/S1474-4422(11)70263-0

Tabrizi, S. J., Scahill, R. I., Durr, A., Roos, R. A., Leavitt, B. R., Jones, R., Landwehrmeyer, G. B., Fox, N. C., Johnson, H., Hicks, S. L., Kennard, C., Craufurd, D., Frost, C., Langbehn, D. R., Reilmann, R., & Stout, J. C. (2011). Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: The 12-month longitudinal analysis. *The Lancet Neurology*, *10*(1), 31–42. https://doi.org/10.1016/S1474-4422(10)70276-3

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., & Langbehn, D. R. (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *The Lancet Neurology*, *12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Telenius, H., Kremer, H. P. H., Thellmann, J., Andrew, S. E., Almqvist, E., Anvret, M., Greenberg, C., Greenberg, J., Lucotte, G., Squltierl, F., Starr, A., Goldberg, Y. P., & Hayden, M. R. (1993). Molecular analysis of juvenile huntington disease: The major influence on (CAG)n repeat length is the sex of the affected parent. *Human Molecular Genetics*, *2*(10), 1535–1540. https://doi.org/10.1093/hmg/2.10.1535

The Huntington's Disease Collaborative Research Group. (1993). A Novel Gene Containing a Trinucleotide

That Is Expanded and Unstable on Huntington's Disease Chromosomes. *Cell*, *72*, 971–983.

Thompson, J. C., Harris, J., Sollom, A. C., Stopford, C. L., Howard, E., Snowden, J. S., & Craufurd, D. (2012). Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *24*(1), 53–60. https://doi.org/10.1176/appi.neuropsych.11030057

Thompson, J. C., Snowden, J. S., Craufurd, D., & Neary, D. (2002). Behavior in Huntington's Disease: Dissociating Cognition-Based and Mood-Based Changes. *Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(1), 37–43.

Trinkler, I., Cleret de Langavant, L., & Bachoud-Lévi, A. C. (2013). Joint recognition-expression impairment of facial emotions in Huntington's disease despite intact understanding of feelings. *Cortex*, *49*(2), 549–558. https://doi.org/10.1016/j.cortex.2011.12.003

van Duijn, E., Kingma, E. M., & van der Mast, R. C. (2007). Psychopathology in verified Huntington's disease gene carriers. *Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(4), 441–448. https://doi.org/10.1176/jnp.2007.19.4.441

van Duijn, E., Reedeker, N., Giltay, E. J., Roos, R. A., & van der Mast, R. C. (2010). Correlates of apathy in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(3), 287–294. https://doi.org/10.1176/jnp.2010.22.3.287

Vinther-Jensen, T., Larsen, I. U., Hjermind, L. E., Budtz-Jørgensen, E., Nielsen, T. T., Nørremølle, A., Nielsen, J. E., & Vogel, A. (2014). A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. *Orphanet Journal of Rare Diseases*, *9*(114), 1–9.

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J.-P. P., & Faull, R. L. M. (2014). Neuropathology in the human brain. In G. P. Bates, L. Jones, & S. J. Tabrizi (Eds.), *Huntington's Disease* (pp. 185–217). Oxford University Press.

Walker, F. O. (2007). Huntington's disease. *Lancet*, *369*, 218–228.

Weinstein, N., Przybylski, A. K., & Ryan, R. M. (2012). The index of autonomous functioning: Development of a scale of human autonomy. *Journal of Research in Personality*, *46*(4), 397–413. https://doi.org/10.1016/j.jrp.2012.03.007

Wibawa, P., Zombor, R., Dragovic, M., Hayhow, B., Lee, J., Panegyres, P. K., Rock, D., & Starkstein, S. E. (2020). Anosognosia Is Associated With Greater Caregiver Burden and Poorer Executive Function in Huntington Disease. *Journal of Geriatric Psychiatry and Neurology*, *33*(1), 52–58. https://doi.org/10.1177/0891988719856697

Appendix | Journal Articles

I Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers. Cognitive and Behavioral Neurology, 34(4), 295–302. https://doi.org/10.1097/WNN.0000000000000286

II Hendel R. K., Hellem M. N. N., Hjermind L. E., Nielsen J. E., & Vogel A. (2022). On the association between apathy and deficits of social cognition and executive functions in Huntington's Disease. Journal of the International Neuropsychological Society. Early Access. https://doi.org/10.1017/S1355617722000364

III Hendel, R. K., Hellem, M. N. N., Larsen, I. U., Vinther-Jensen, T., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2022). Impairments of social cognition significantly predict the progression of functional decline in Huntington's disease: A 6-year follow-up study. Applied Neuropsychology: Adult. Early Access. https://doi.org/10.1080/23279095.2022.2073824

IV Hendel R. K., Hellem M. N. N., Hjermind L. E., Nielsen J. E., & Vogel A. (2022). An Exploratory Study Investigating Autonomy in Huntington Disease Gene Expansion Carriers. Journal of Huntington's Disease. Early Access. https://doi.org/10.3233/JHD-220540

MANUSCRIPT I

Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers. Cognitive and Behavioral Neurology, 34(4), 295–302.
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Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers

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Background: Apathy is a prevalent behavioral syndrome of Huntington disease (HD) that can result in severe loss of function for the individual with HD and substantial caregiver distress. Research-based evidence of apathy is characterized by methodological differences, and there is a deficiency in the evidence concerning the subtypes of apathy.

Objective: To characterize apathy in premanifest and motor-manifest HD gene expansion carriers and controls using the Short Problem Behaviors Assessment for Huntington's Disease (PBA–s) and the Lille Apathy Rating Scale (LARS).

Method: We included 82 HD gene expansion carriers (premanifest and motor manifest) and 32 controls (Mini-Mental State Examination score ≥24 and Montreal Cognitive Assessment score ≥19) in the study. We quantified apathy using the PBA–s and the LARS and performed correlation analyses between the global LARS score and motor function, cytosine-adenine-guanine repeat length, cytosine-adenine-guanine Age Product score, and neuropsychiatric and cognitive symptoms.

Results: The motor-manifest HD gene expansion carriers scored significantly higher than the controls on the global score and the Intellectual Curiosity and Action Initiation subscales of the LARS. Apathy was present in 28% of the HD gene expansion carriers (including 7 premanifest). The apathetic participants had a significantly higher motor score, significantly higher scores on the neuropsychiatric instruments, and significantly lower cognitive scores compared with the controls.

Conclusion: Apathy is a frequent syndrome that is found in individuals with HD. Apathy has a specific expression, with symptoms such as reduced initiation, voluntary actions, and interests, that might be related to the underlying neuropathology. Apathy is related to disease progression, neuropsychiatric symptoms, and cognitive impairments.

Key Words: Huntington disease, apathy, apathy subtypes, behavioral symptoms

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CAG = cytosine-adenine-guanine. **CAP** = cytosine-adenine-guanine Age Product. **HAM–17** = Hamilton Depression Scale–17. **HC** = healthy controls. **HD** = Huntington disease. **LARS** = Lille Apathy Rating Scale. **MMSE** = Mini-Mental State Examination. **MoCA** = Montreal Cognitive Assessment. **PBA–s** = The Short Problem Behaviors Assessment for Huntington's Disease. **PD** = Parkinson disease. **SCL-90–R** = Symptom Checklist 90—Revised. **TMS** = Total Motor score. **UHDRS** = Unified Huntington's Disease Rating Scale.

Huntington disease (HD) is an autosomal-dominant inherited neurodegenerative disease that is caused by an expansion of the cytosine-adenine-guanine (CAG) repeat in the huntingtin gene on chromosome 4 (The Huntington's Disease Collaborative Research Group, 1993; Walker, 2007). Clinical manifestations of HD include motor disturbances, neuropsychiatric symptoms, and cognitive deterioration (McColgan and Tabrizi, 2018). Behavioral symptoms that cause substantial distress in the daily life of both individuals with HD and their caregivers include irritability, psychosis, affective symptoms, perseveration, and apathy (Craufurd et al, 2001; Eddy et al, 2016).

Apathy involves a lack of initiative, a loss of voluntary and goal-directed behavior, and emotional flattening (Andrews et al, 2020; Camacho et al, 2018). It is one of the most frequent and distressing symptoms found in individuals with HD, with a worldwide prevalence ranging from 34% to 76% (van Duijn et al, 2007). Apathy in individuals with HD is associated with older age; male sex; higher Total Motor score (TMS) and lower Total Functional Capacity score on the Unified Huntington's Disease Rating Scale (UHDRS; Huntington Study Group, 1996);

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and poorer executive functions, attention, psychomotor speed, and global cognition (Andrews et al, 2020; Baudic et al, 2006; van Duijn et al, 2010).

Researchers have proposed that the presence of apathy in individuals with HD is a marker of disease progression (Camacho et al, 2018; Thompson et al, 2012) and a predictor of cognitive impairments (Andrews et al, 2020; Baudic et al, 2006). Similarly, apathy has been closely linked to disease progression and cognitive impairments in individuals with other neurodegenerative diseases such as Alzheimer disease and Parkinson disease (PD) (Dujardin et al, 2009; Starkstein et al, 2006). However, apathy should not be considered a single symptom, but rather a syndrome that encompasses several subtypes.

Levy and Dubois (2006) explained the presence of apathy by neuropathological changes in the circuitry of the prefrontal cortex and subregions within the basal ganglia. They proposed that the disruption of three different processing mechanisms (auto-activation, cognitive, and emotional–affective processing) could lead to differentiated symptoms of apathy, each of which presents with a unique neuropathological signature. This division of apathy symptoms into three domains has been supported by other theoretical models (Robert et al, 2009; Starkstein and Leentjens, 2008).

De Paepe et al (2019) examined the white matter tracts involved in these processing mechanisms in individuals with HD and found that HD gene expansion carriers with increased mean diffusivity in the right frontostriatal tract and the left dorsolateral prefrontal cortex to caudate nucleus tract had a higher degree of cognitive apathy, whereas HD gene expansion carriers with increased mean diffusivity in the right uncinate fasciculus had a higher degree of impairments in auto-activation processing. Thus, the presence of apathy subtypes is substantiated by the neuropathological changes involved, but to date, subtypes of apathy in individuals with HD is still a topic that has received little attention.

The body of evidence concerning apathy in individuals with HD is affected by variability in its characterization in addition to differences in the methodology and instruments used for examination. These inconsistencies pose a challenge to the generalizability of previous results. A widely used and validated clinical instrument for examining apathy is the Short Problem Behaviors Assessment for Huntington's Disease (PBA–s; Callaghan et al, 2015; Craufurd et al, 2001), but the PBA–s includes only one item on apathy. Consequently, the scale differentiates poorly between the severity of apathy or any subtypes of apathy. In a review by Mestre et al (2016) on scales measuring behavioral symptoms in individuals with HD, the PBA–s was simply "suggested" for use as a screening instrument when following the criteria recommended by the International Parkinson and Movement Disorder Society. Moreover, there was no recommendation for scales that are directed solely at examining apathy.

The Lille Apathy Rating Scale (LARS; Sockeel et al, 2006) has been proposed as a functional and sound instrument of apathy that might be useful in the examination of apathy in individuals with HD. The LARS was originally developed to examine apathy in individuals with PD within a broad range of disease stages (Sockeel et al, 2006) and has been shown to be a reliable and valid instrument for examining apathy in individuals with dementia, even in the early stages of the disease (Fernández-Matarrubia et al, 2016).

We aimed to investigate if differences in apathy could be found in premanifest and motor-manifest HD gene expansion carriers relative to healthy controls (HC). Our objective was to characterize apathy in premanifest and motor-manifest HD gene expansion carriers by examining the frequency and subtypes of apathy in HD gene expansion carriers and by investigating the association between the global LARS score and the UHDRS TMS, CAG-repeat length, CAG Age Product (CAP) score, neuropsychiatric symptoms, and cognitive functions. We further wished to examine which of the three symptom groups—motor function, neuropsychiatric functions, and cognitive functions—could explain the global LARS score. Finally, we wished to determine the correlation between apathy as examined with the PBA–s and with the LARS.

METHOD

Participants

This study was part of a larger prospective cohort study on HD that took place at the neurogenetics clinic of the Danish Dementia Research Centre in Rigshospitalet, Denmark. We included HD gene expansion carriers who had previously participated in a study at our clinic (Vinther-Jensen et al, 2014) or who had responded to an advertisement in the newsletter of the Danish Huntington's Disease Association. Recruitment took place from June 2017 to June 2020. Individuals were included in the present study if they had a CAG-repeat length of ≥39 repeats, a Mini-Mental State Examination (MMSE; Folstein et al, 1975) score of ≥24, and a Montreal Cognitive Assessment (MoCA; Nasreddine et al, 2005) score of ≥19. Exclusion criteria included other neurologic illness, ongoing alcohol or drug abuse, or a native language other than Danish.

We included a control group consisting of family members who had previously been at risk for inheriting HD but who had tested negative for the gene expansion (with a CAG-repeat length of <30 repeats). We chose this group over unrelated HC to better match for psychosocial and environmental factors. All of the participants received genetic counseling and information on their genetic status before, and independently from, study enrollment.

The study protocol was approved by the ethics committee of the Capital Region of Denmark and was performed according to the ethical guidelines of the Declaration of Helsinki and its later amendments. All individuals provided informed written consent before enrolling in the study.

Assessments

All of the individuals who took part in the larger HD study had a minimum of two planned visits, during which

they completed a neurologic, neuropsychiatric, and neuropsychological examination. The order of the visits to which individuals were enrolled in the study was random: Some individuals started with the neurologic examination; others started with the neuropsychological examination. The initial screening tests (ie, MMSE and MoCA) were performed at the first visit in order to make sure the individuals were eligible for the study. All of the examinations were performed by the same physician (M.N.N.H.) and neuropsychologist (R.K.H.). In this study, we report on the results that are relevant for the assessment of apathy in individuals with HD.

Neurologic and Neuropsychiatric Examination

We assessed the motor performance of each of the participants using the UHDRS TMS. The standardized rating of motor symptoms on the UHDRS TMS yields a total score between 0 and 124, where a higher score indicates more pronounced motor impairments. We assessed the neuropsychiatric symptoms of each of the participants using the Symptom Checklist 90—Revised (SCL-90–R; Derogatis, 2009) and the Hamilton Depression Scale–17 (HAM–17; Hamilton, 1960).

The SCL-90–R is designed to reflect the current status of one's psychological distress (Derogatis, 2009). It is a self-report inventory with 90 items, each item representing a psychological symptom, and is rated on a 5-point Likert scale ranging from *not at all* to *extremely* distressing. The SCL-90–R describes nine primary symptom dimensions and three global indices of distress. We used the Global Severity Index to assess each individual's neuropsychiatric distress. Raw scores were converted to T scores, normalized to a Danish sample of nonpsychiatric participants sorted by gender (Olsen et al, 2004). The HAM–17 is a semistructured interview, covering 17 symptom areas of depression. All of the instruments were filled out at the clinic by the study participants with the help of M.N.N.H.

Short Problem Behaviors Assessment for Huntington's Disease. We assessed the behavioral symptoms of each of the participants using the PBA–s. The PBA–s is a semistructured interview that contains 11 items that assess different behavioral problems related to HD. Each item describes a behavioral symptom, which is rated on a 5-point Likert scale ranging from 0 (*absent*) to 4 (*present all the time/causing severe problems*) for both the severity and the frequency of the behavior. The ratings are based on all relevant information—from the patient, an informant (eg, caregiver or family member), and the clinician's own observations (Callaghan et al, 2015).

The PBA–s contains one item on apathy, incorporating four clinical aspects from the original Problem Behaviors Assessment for HD (Craufurd et al, 2001). For each behavioral symptom, an overall symptom score is calculated by multiplying the severity rating by the frequency rating. Hence, the Apathy subscale score, which we used in the present study, is a product score for apathy that is based on the multiplication of the scores.

No clear cutoff has been suggested for classifying individuals with apathy using the PBA–s. In some studies, a cutoff of ≥ 2 on the severity score of the apathy item is used to indicate the presence of apathy (Andrews et al, 2020; Thompson et al, 2012). In the present study, we used the product score, or the Apathy subscale score, of ≥ 2 as the cutoff.

Neuropsychological Assessment

As part of an extensive neuropsychological assessment, we examined the participants with the LARS, separate from and without knowledge of the individuals' PBA–s scores. The neuropsychological examination was part of the larger study on HD in our clinic, and the results will be reported elsewhere.

Lille Apathy Rating Scale. The LARS is a standardized structured interview that contains 33 items divided into nine domains. The first 3 items are coded on a 5-point Likert scale (–2; 2). Items 4–33 are positively worded questions that are coded on a binary yes/no scale (–1; 1), with an additional NA (0, not answerable) for nonapplicable items. Based on the participants' answers, we computed a global score of –36 to 36, representing an individual's degree of apathy, with a higher score indicating more apathetic behavior. We also computed four subtypes of apathy (Intellectual Curiosity, Emotion, Action Initiation, and Self Awareness), each with an average score of –4 to 4. The score of each subtype represented the average score of the domains within that subtype. Please see Sockeel et al (2006) for more information.

Based on the HC data, we calculated regression-based reference data for the global LARS score, correcting for age, sex, and Educational Index score. As specified by the regression model, we calculated percentile estimates for the expected scores as the inverse of the normal cumulative distribution function. Each of the individual's observed score was compared with the estimated score from the relevant group. An individual was classified as apathetic if his or her score was $\leq$10th-percentile estimate. This method has previously been used on other types of data (Vogel et al, 2018, 2020).

Statistical Analysis

We performed all statistical analyses using SPSS version 25. Group comparisons were analyzed with a one-way ANOVA or with the Kruskal-Wallis test based on variance heterogeneity with a 5% alpha level (two-tailed significance) and followed by the Dunnett post hoc test when applicable. We used the Mann-Whitney U test for group comparisons with skewed distributions. The Bonferroni-Holm correction was applied when multiple comparisons were performed to adjust the level of significance. We calculated effect sizes using the formula denoted by Field (2018): $r = \frac{z}{\sqrt{N}}$. A CAP score was calculated as CAP = Age (CAG − 35.5) for each HD gene expansion carrier (Penney et al, 1997).

We used correlation analyses to analyze the associations with demographic data, and we performed Pearson r or Spearman ρ (for skewed distributions) to examine the

level of significance. Finally, we constructed a linear regression model with the global LARS score as the outcome variable in order to investigate which symptom groups could best explain the presence of apathy. We entered one variable from each of the three symptom groups—motor function, neuropsychiatric functions, and cognitive functions—into the model, based on the correlation coefficients with the highest effect.

RESULTS

Participants

One-hundred fourteen HD gene expansion carriers and 32 HC volunteered to participate in the study. We excluded 32 of the HD gene expansion carriers because their performance on the initial screening tests was outside the inclusion criteria or they did not take part in both visits. This left us with a final number of 82 HD gene expansion carriers. We assigned a classification of premanifest HD gene expansion carrier if their UHDRS TMS was ≤5 (n = 40), with no substantial motor signs, and a classification of motor-manifest HD gene expansion carrier if their UHDRS TMS was >5 (n = 42).

Assessments

Background information on the HD gene expansion carriers and the HC is presented in Table 1, together with their performance on the cognitive screening, motor, and neuropsychiatric instruments. The premanifest HD gene expansion carriers had a significantly lower score on the cognitive screening instruments compared with the HC, although effect sizes revealed a small effect only (MMSE: $r = 0.23$, MoCA: $r = 0.21$). The motor-manifest HD gene expansion carriers had a significantly lower score on the cognitive screening instruments and a significantly higher score on the UHDRS TMS and the SCL-90–R when compared with both the premanifest HD gene expansion carriers and the HC.

TABLE 1. Background Information and Results From the Cognitive Screening, Motor, and Neuropsychiatric Instruments for the HD Gene Expansion Carriers and the HC

	HD Gene Expansion Carriers		
	Premanifest	Motor Manifest	HC
N	40	42	32
Age (years)	41.3 (11.0)	52.5 (12.3)‡	48.1 (14.1)
Sex (male/female)	24/16	22/20	13/19
Educational Index score	14.5 (1.8)	12.9 (1.8)†‡	14.7 (1.9)
CAG-repeat length	41.8 (2.4)†	42.7 (2.5)†	19.8 (4.0)
CAP score	248.7 (80.3)	361.1 (92.3)‡	—
MMSE score	28.8 (1.1)†	27.4 (1.9)†‡	29.3 (1.1)
MoCA score	28.1 (2.0)†	25.4 (2.9)†‡	29.2 (1.2)
UHDRS TMS	1.5 (1.5)	24.1 (14.4)†‡	1.3 (1.3)
HAM–17 score	2.5 (3.1)	4.2 (3.6)	2.7 (3.0)
SCL-90–R GSI	42.0 (10.1)	51.1 (12.1)†‡	43.7 (11.2)

Values are presented as M ± SD unless noted otherwise.
†Statistically significant difference from the HC ($P < 0.05$).
‡Statistically significant difference from the individuals with premanifest HD ($P < 0.05$).
CAG = cytosine-adenine-guanine. **CAP** = CAG Age Product. **GSI** = Global Severity Index. **HAM–17** = Hamilton Depression Scale–17. **HC** = healthy controls. **HD** = Huntington disease. **MMSE** = Mini-Mental State Examination. **MoCA** = Montreal Cognitive Assessment. **SCL-90–R** = Symptom Checklist 90—Revised. **TMS** = Total Motor score. **UHDRS** = Unified Huntington's Disease Rating Scale.

The PBA–s and the LARS

The results of the HD gene expansion carriers and the HC on the PBA–s Apathy subscale and on the LARS are presented in Table 2. The motor-manifest HD gene expansion carriers had a significantly higher PBA–s Apathy subscale score compared with the premanifest HD gene expansion carriers and the HC. Effect sizes revealed medium-sized effects ($r = –0.37$, $r = 0.42$, respectively). Likewise, the motor-manifest HD gene expansion carriers had a significantly higher global LARS score compared with the premanifest HD gene expansion carriers and the HC. Effect sizes revealed medium-sized effects ($r = 0.31$, $r = –0.42$, respectively).

The Intellectual Curiosity and Action Initiation subscale scores were significantly higher for the motor-manifest HD gene expansion carriers compared with the HC ($P = 0.006$, $P < 0.001$, respectively). When comparing the premanifest with the motor-manifest HD gene expansion carriers, there was a significant difference between the two groups on Intellectual Curiosity ($P = 0.048$) and Action Initiation ($P < 0.001$). However, after correcting

TABLE 2. Performance on the PBA–s Apathy Subscale and on the LARS for the HD Gene Expansion Carriers and the HC

	HD Gene Expansion Carriers		
	Premanifest	Motor Manifest	HC
N	40	42	32
PBA–s Apathy subscale score	0.1 (0.2)	1.2 (2.0)†‡	0.1 (0.3)
Global LARS score	−25.2 (4.3)	−21.2 (6.7)†‡	−26.3 (3.0)
Intellectual Curiosity score	−2.8 (0.7)	−2.4 (0.9)†	−2.9 (0.5)
Emotions score	−2.6 (1.0)	−2.3 (1.0)	−2.6 (0.7)
Action Initiation score	−3.4 (0.7)	−2.4 (1.1)†‡	−3.5 (0.6)
Self-Awareness score	−2.1 (1.8)	−2.3 (1.6)	−2.5 (1.5)

Values are presented as M ± SD unless noted otherwise.
†Statistically significant difference from the HC ($P < 0.05$).
‡Statistically significant difference from the individuals with premanifest HD ($P < 0.05$).
HC = healthy controls. **HD** = Huntington disease. **LARS** = Lille Apathy Rating Scale. **PBA–s** = Short Problem Behaviors Assessment for Huntington's Disease.

for multiple comparisons, the difference on Intellectual Curiosity could not be considered significant. Effect sizes for the difference between the motor-manifest and premanifest HD gene expansion carriers and the HC on Intellectual Curiosity were small to medium ($r = 0.22$, $r = –0.34$, respectively) and on Action Initiation were medium to large ($r = 0.48$, $r = –0.51$, respectively). The premanifest HD gene expansion carriers did not differ significantly from the HC on any of the apathy instruments.

Association With Symptom Groups

When we examined the total group of HD gene expansion carriers, we found significant negative correlations between the global LARS score and scores on the cognitive screening instruments (MMSE: $\rho = –0.23$, $P = 0.041$, MoCA: $r = –0.25$, $P = 0.024$). Significant positive correlations were found between the global LARS score and the UHDRS TMS ($\rho = 0.36$, $P = 0.001$). Significant positive correlations were also found between the global LARS score and scores on the neuropsychiatric instruments (SCL-90–R Global Severity Index: $r = 0.30$, $P = 0.007$, HAM–17: $\rho = 0.40$, $P < 0.001$). In contrast, no significant correlations were found between the global LARS score and age, CAG-repeat length, or CAP score.

A linear regression model was constructed, with one variable entered from each symptom group (motor function, neuropsychiatric functions, and cognitive functions) and the global LARS score as the outcome variable. From the neuropsychiatric and cognitive symptom groups, we selected the variables with the highest correlation coefficients (MoCA score and HAM–17 score, respectively). The linear regression model showed that the UHDRS TMS and the HAM–17 score were significant predictors of the global LARS score, whereas the effect of the MoCA score was small and insignificant (constant = –24.56 $SE_{constant} = 7.55$, CI = [–39.60; –9.52], $P = 0.002$, $b_{UHDRS} = 0.12$, $SE_{UHDRS} = 0.05$, CI = [0.02; 0.22], $P = 0.022$, $b_{MoCA} = –0.06$, $SE_{MoCA} = 0.27$, CI = [–0.59; 0.47], $P = 0.819$, $b_{HAM\text{-}17} = 0.43$, $SE_{HAM\text{-}17} = 0.19$, CI = [0.06; 0.81], $P = 0.023$). This model explained 21% of the total variance of the global LARS score ($R^2 = 0.21$, $P < 0.001$).

Apathetic and Nonapathetic Participants

Group comparisons between the apathetic and nonapathetic HD gene expansion carriers are presented in Table 3. When we used regression-based cutoff scores on the global LARS score, we found a frequency of 28% for the HD gene expansion carriers. With this method, we classified seven premanifest and 16 motor-manifest HD gene expansion carriers as apathetic and the remainder as nonapathetic. The apathetic HD gene expansion carriers had significantly higher UHDRS TMSs than the nonapathetic HD gene expansion carriers and scored significantly higher on the neuropsychiatric instruments (SCL-90–R Global Severity Index and HAM–17). In contrast, we found no significant differences in CAG-repeat length or CAP score between the apathetic and nonapathetic HD gene expansion carriers.

When compared with the HC, the apathetic HD gene expansion carriers had significantly lower scores on the cognitive screening instruments and significantly higher scores on the neuropsychiatric instruments. The nonapathetic HD gene expansion carriers also differed significantly from the HC on most of the instruments except for the SCL-90–R Global Severity Index score and the HAM–17 score.

TABLE 3. Performance Scores for the Apathetic and Nonapathetic HD Gene Expansion Carriers, as Classified by the LARS, and the HC

	HD Gene Expansion Carriers		
	Apathetic	**Nonapathetic**	**HC**
N	23	59	32
UHDRS TMS	21.3 (18.3)†‡	9.9 (12.9)†	1.3 (1.3)
CAG-repeat length	42.4 (2.5)†	42.2 (2.5)†	19.8 (4.0)
CAP score	314.7 (82.7)	303.0 (110.3)	—
MMSE score	27.3 (2.0)†	28.4 (1.5)†	29.3 (1.1)
MoCA score	25.6 (3.5)†	27.2 (2.5)†	29.2 (1.2)
HAM–17 score	5.3 (4.5)†‡	2.6 (2.5)	2.7 (3.0)
SCL-90–R GSI	52.4 (13.5)†‡	44.5 (10.6)	43.7 (11.2)

Values are presented as M ± SD unless noted otherwise.
†Statistically significant difference from the HC ($P < 0.05$).
‡Statistically significant difference from the nonapathetic HD gene expansion carriers ($P < 0.05$).
CAG = cytosine-adenine-guanine. **CAP** = CAG Age Product. **GSI** = Global Severity Index. **HAM–17** = Hamilton Depression Scale–17. **HC** = healthy controls. **HD** = Huntington disease. **LARS** = Lille Apathy Rating Scale. **MMSE** = Mini-Mental State Examination. **MoCA** = Montreal Cognitive Assessment. **SCL-90–R** = Symptom Checklist 90—Revised. **TMS** = Total Motor score. **UHDRS** = Unified Huntington's Disease Rating Scale.

When applying a cutoff on the PBA–s Apathy subscale score of ≥2, 12 HD gene expansion carriers had some degree of apathy, corresponding to a frequency of 14.6%. There was a significant small to medium correlation between the PBA–s Apathy subscale score and the global LARS score ($\rho = 0.31$, $P = 0.005$) in the total group of HD gene expansion carriers.

DISCUSSION

In this study, we examined apathy in HD gene expansion carriers and HC using the PBA–s and the LARS. The results showed that the global LARS score and the Intellectual Curiosity and Action Initiation subscale scores differed significantly between the groups, with motor-manifest HD gene expansion carriers having significantly higher scores than the HC. These results indicate a higher degree of apathy among the motor-manifest HD gene expansion carriers and are consistent with several previous studies on apathy in individuals with HD, where symptoms increase over the course of the disease, presumably following the progression of HD (Thompson et al, 2002, 2012; van Duijn et al, 2007).

When we compared the impairments examined by the items of Intellectual Curiosity and Action Initiation to

the impairments involved in the framework by Levy and Dubois (2006), we found a correspondence to the impairments of diminished auto-activation/goal-directed behavior and cognitive apathy, with symptoms such as reduced initiation, voluntary actions, and interests. This finding is in accordance with the study by De Paepe and colleagues (2019), where impairments of auto-activation and cognitive apathy were found for individuals with manifest HD compared with HC. This finding suggests that the symptoms of apathy that are exhibited by individuals with HD have a specific expression that may be related to the underlying neuropathology. This result underlines the importance of examining the subtypes of apathy in individuals with HD more comprehensively in the clinic because this knowledge could be beneficial for the development of future therapeutic approaches.

According to Levy and Dubois (2006), the neuropathological changes involved in the impairments of auto-activation and cognitive apathy include areas of the frontal cortex, dorsolateral and medial prefrontal cortex, caudate nucleus, internal part of the globus pallidus, medial–dorsal thalamus, substantia nigra, and thalamic nuclei. These areas are consistent with the changes in white matter tracts that were found by De Paepe and colleagues (2019) and overlap with the early neuropathological changes in individuals with HD, where atrophy in the striatal and cortical areas, and dysfunction of the cortico-basal ganglia-thalamo-cortico circuits, is found (Mehrabi et al, 2016).

The frequency of apathy among our HD gene expansion carriers was 28% when it was examined with the LARS, which is somewhat lower than otherwise reported in the literature (van Duijn et al, 2007). One likely explanation for this discrepancy is that the present study involved HD gene expansion carriers in the premanifest stage of the disease, whereas the van Duijn et al (2007) study did not. Because there seems to be a progressive worsening of apathy over time (Thompson et al, 2012), including the premanifest HD gene expansion carriers in the present study might have affected the frequency rate of apathy. When we calculated the frequency based on the motor-manifest HD gene expansion carriers only, we found a comparable level of 38%. Moreover, the frequency corresponds to the 29% that was reported in the validation study of the LARS with individuals with PD (Sockeel et al, 2006).

The proposed cutoff for apathy in the Sockeel and colleagues (2006) study was –16. This cutoff was lower than the regression-based cutoffs we used in the present study, which varied between –23; –17 for men and –24; –17 for women, depending on age and education level. The HC group used in the present study was well educated and included a small number of individuals; therefore, our HC group should not be considered representative of the normal population. Sockeel and colleagues (2006) proposed a cutoff of –22; –17 for slightly apathetic symptoms, which is comparable to the cutoffs we used in the present study. Thus, the level of apathy in individuals with HD seems to be comparable to the level found in individuals with PD (Sockeel et al, 2006). This finding is in line with a previous study that found comparable prevalence of apathy in individuals with PD and those with HD, although the type of apathy differed between the two groups (Sousa et al, 2018).

While the frequency of apathy in the present study corresponded somewhat with what was found in previous studies, there was a large difference between the frequency on the PBA–s Apathy subscale and on the global LARS score. We found a significant correlation between the PBA–s Apathy subscale score and the global LARS score, but this correlation was small to medium sized ($\rho = 0.31$). This finding is interesting given the assumption that both instruments examine the same construct. As mentioned in the introduction, the body of evidence concerning apathy in individuals with HD varies considerably according to the methodology used in a study, particularly the instruments that are used to examine apathy. This result illustrates the variability between the instruments, and it should be noted that results on apathy should not be compared directly between different instruments.

We found that the global LARS score was significantly correlated with the UHDRS TMS and was correlated with the results on the cognitive screening and neuropsychiatric instruments. The association between apathy and cognitive impairments has been found in several studies both in individuals with HD (Andrews et al, 2020; Baudic et al, 2006; Camacho et al, 2018) and in individuals with other neurodegenerative diseases, such as Alzheimer disease and PD (Dujardin et al, 2009; Starkstein et al, 2006). Researchers have proposed that the association between apathy and cognitive impairments is a result of both symptom groups arising from striatal degeneration and disruption of the frontal–striatal circuits (Andrews et al, 2020; Thompson et al, 2002). On the other hand, no clear association has been found between apathy and other neuropsychiatric symptoms in individuals with HD, except depression (van Duijn et al, 2010).

The linear regression model revealed that the UHDRS TMS and the HAM–17 score were significant predictors of the global LARS score, whereas the MoCA score did not contribute significantly to the model. The predictive value of the HAM–17 score was expected because depression and apathy are highly associated, and discrimination between these phenomena is a continuous discussion. Accordingly, the association between depressive symptoms and apathy in individuals with HD has been found previously (Andrews et al, 2020; Thompson et al, 2002; van Duijn et al, 2010), but it has been suggested that depression is not associated with disease duration nor is it a predictor of disease progression as apathy has been found to be (Craufurd et al, 2001; Thompson et al, 2002). Apathy can be present without depression, and depression can be present without apathy (Thompson et al, 2002).

That the UHDRS TMS was entered as a predictive variable when seen as a proxy of disease progression was in agreement with previous studies, where apathy was found to be a marker of disease progression (Camacho

et al, 2018; Thompson et al, 2012). Thus, apathy seemed to follow the progression of the disease in the present study also. We found that seven of the 23 participants who were classified as apathetic were premanifest HD gene expansion carriers. A speculative interpretation might be that apathy was among the earliest symptoms of disease in these individuals. The fact that the CAP score was not significantly correlated with the global LARS score, and that the apathetic HD gene expansion carriers did not have a significantly higher CAP score than the non-apathetic carriers, indicates that disease burden does not predict the degree of apathy.

Study Limitations

A limitation linked to the LARS is the self-reported nature of the instrument. HD gene expansion carriers can have a lack of insight into their own inabilities (McCusker and Loy, 2014), and this impaired awareness of deficits may also include a lack of insight in apathy because apathy and impaired awareness of deficits are both related to dysfunction in the frontal–subcortical circuitry (Duff et al, 2010). Because this study did not include a measure of insight, the apathy scores may have been distorted by a lack of insight. A lack of insight could be another explanation for the low frequency of apathy in the motor-manifest HD gene expansion carriers in the present study.

In contrast, the PBA–s includes the perceptions of the patient, caregiver, and clinician in every score and therefore is not influenced by a possible lack of insight. Because the prevalence of apathy as examined by the PBA–s was lower than the prevalence of apathy as examined by the LARS, a lack of insight may not have affected the results of the LARS to a large degree. In recent studies, it has been shown that HD gene expansion carriers in the early stages of the disease are aware of their degree of apathy (Atkins et al, 2021; Baake et al, 2018). Thus, we hypothesize that impaired awareness of deficits was only a limited confounder in our study.

It should be noted that the eventual pharmacological treatment of the participants was not controlled for and might have affected the present results. However, unlike the participants in Sockeel and colleagues (2006), the present study only included individuals in the early stages of the disease and therefore we would not expect them to receive treatment that could have affected the examination of their apathy symptoms to a large degree.

CONCLUSION

When examined with the LARS, the motor-manifest HD gene expansion carriers had a significantly higher degree of apathy compared with the premanifest HD gene expansion carriers and the HC. In addition, scores on two of the four subtypes of apathy on the LARS were significantly higher for the motor-manifest HD gene expansion carriers compared with the HC. We suggest that apathy in individuals with HD has a specific expression, with symptoms such as reduced initiation, voluntary actions, and interests, that might be related to the underlying neuropathology.

The frequency of apathy was 14.6% among the HD gene expansion carriers when examined with the PBA–s Apathy subscale and 28% when examined with the global LARS. There was a significant correlation between the PBA–s Apathy subscale score and the global LARS score in the HD gene expansion carriers, but it was weaker than expected given that the two instruments should examine the same construct. The UHDRS TMS and the HAM–17 score had a significant impact on the global LARS score. Thus, the LARS is a functional and sound instrument that allows a comprehensive examination of apathy in HD gene expansion carriers.

REFERENCES

Andrews SC, Langbehn DR, Craufurd D, et al. 2020. Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychol Med*. 17:1–7. doi:10.1017/S0033291720000094

Atkins KJ, Andrews SC, Chong TTJ, et al. 2021. Multidimensional apathy: the utility of the Dimensional Apathy Scale in Huntington's disease. *Mov Disord Clin Pract*. 8:361–370. doi:10.1002/mdc3.13147

Baake V, van Duijn E, Roos RAC. 2018. Huntington's disease gene expansion carriers are aware of their degree of apathy. *J Neuropsychiatry Clin Neurosci*. 30:183–187. doi:10.1176/appi.neuropsych.18020031

Baudic S, Maison P, Dolbeau G, et al. 2006. Cognitive impairment related to apathy in early Huntington's disease. *Dement Geriatr Cogn Disord*. 21:316–321. doi:10.1159/000091523

Callaghan J, Stopford C, Arran N, et al. 2015. Reliability and factor structure of the Short Problem Behaviors Assessment for Huntington's Disease (PBA–s) in the TRACK-HD and REGISTRY studies. *J Neuropsychiatry Clin Neurosci*. 27:59–64. doi:10.1176/appi.neuropsych.13070169

Camacho M, Barker RA, Mason SL. 2018. Apathy in Huntington's disease: a review of the current conceptualization. Published online March 28. *J Alzheimer's Dis Parkinsonism*. 8:1–9. doi:10.4172/2161-0460.1000431

Craufurd D, Thompson JC, Snowden JS. 2001. Behavioral changes in Huntington disease. *Neuropsychiatry Neuropsychol Behav Neurol*. 14:219–226.

De Paepe AE, Sierpowska J, Garcia-Gorro C, et al. 2019. White matter cortico-striatal tracts predict apathy subtypes in Huntington's disease. Published online July 30. *NeuroImage Clin*. 24:101965. doi:10.1016/j.nicl.2019.101965

Derogatis LR. 2009. *SCL-90–R Symptom Checklist-90–R Dansk Version*. Copenhagen, Denmark: Pearson.

Duff K, Paulsen JS, Beglinger LJ, et al. 2010. "Frontal" behaviors before the diagnosis of Huntington's disease and their relationship to markers of disease progression: evidence of early lack of awareness. *J Neuropsychiatry Clin Neurosci*. 22:196–207. doi:10.1176/jnp.2010.22.2.196

Dujardin K, Sockeel P, Delliaux M, et al. 2009. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Mov Disord*. 24:2391–2397. doi:10.1002/mds.22843

Eddy CM, Parkinson EG, Rickards HE. 2016. Changes in mental state and behaviour in Huntington's disease. *Lancet Psychiatry*. 3:1079–1086. doi:10.1016/S2215-0366(16)30144-4

Fernández-Matarrubia M, Matías-Guiu JA, Moreno-Ramos T, et al. 2016. Validation of the Lille's Apathy Rating Scale in very mild to moderate dementia. *Am J Geriatr Psychiatry*. 24:517–527. doi:10.1016/j.jagp.2015.09.004

Field A. 2018. Non-parametric models. In: Field A, ed. *Discovering Statistics Using IBM SPSS Statistics*. 5th ed. London, United Kingdom: SAGE; 281–332.

Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 12:189–198. doi:10.3744/snak.2003.40.2.021

Hamilton M. 1960. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 23:56–62. doi:10.1136/jnnp.23.1.56

Huntington Study Group. 1996. Unified Huntington's Disease Rating Scale: reliability and consistency. *Mov Disord*. 11:136–142. doi:10.1002/mds.870110204

The Huntington's Disease Collaborative Research Group. 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 72:971–983. doi:10.1016/0092-8674(93)90585-E

Levy R, Dubois B. 2006. Apathy and the functional anatomy of the prefrontal cortex–basal ganglia circuits. *Cereb Cortex*. 16:916–928. doi:10.1093/cercor/bhj043

McColgan P, Tabrizi SJ. 2018. Huntington's disease: a clinical review. *Eur J Neurol*. 25:24–34. doi:10.1111/ene.13413

McCusker E, Loy CT. 2014. The many facets of unawareness in Huntington disease. Published online November 12. *Tremor Other Hyperkinet Mov (N Y)*. 4:257. doi:10.7916/D8FJ2FD3

Mehrabi NF, Singh-Bains MK, Waldvogel R, et al. 2016. Cortico-basal ganglia interactions in Huntington's disease. Published online July 21. *Ann Neurodegener Disord*. 1:1007.

Mestre TA, van Duijn E, Davis AM, et al. 2016. Rating scales for behavioral symptoms in Huntington's disease: critique and recommendations. *Mov Disord*. 31:1466–1478. doi:10.1002/mds.26675

Nasreddine ZS, Phillips NA, Bédirian V, et al. 2005. The Montreal Cognitive Assessment (MoCA): a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 53:695–699. doi:10.1111/j.1532-5415.2005.53221

Olsen LR, Mortensen EL, Bech P. 2004. The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. *Acta Psychiatr Scand*. 110:225–229. doi:10.1111/j.1600-0447.2004.00399.x

Penney JB Jr, Vonsattel JP, MacDonald ME, et al. 1997. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol*. 41:689–692. doi:10.1002/ana.410410521

Robert P, Onyike CU, Leentjens AFG, et al. 2009. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry*. 24:98–104. doi:10.1016/j.eurpsy.2008.09.001

Sockeel P, Dujardin K, Devos D, et al. 2006. The Lille Apathy Rating Scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 77:579–584. doi:10.1136/jnnp.2005.075929

Sousa M, Moreira F, Jesus-Ribeiro J, et al. 2018. Apathy profile in Parkinson's and Huntington's disease: a comparative cross-sectional study. *Eur Neurol*. 79:13–20. doi:10.1159/000481981

Starkstein SE, Jorge R, Mizrahi R. 2006. The prevalence, clinical correlates and treatment of apathy in Alzheimer's disease. *Eur J Psychiatry*. 20:96–106. doi:10.4321/S0213-61632006000200005

Starkstein SE, Leentjens AFG. 2008. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry*. 79:1088–1092. doi:10.1136/jnnp.2007.136895

Thompson JC, Harris J, Sollom AC, et al. 2012. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 24:53–60. doi:10.1176/appi.neuropsych.11030057

Thompson JC, Snowden JS, Craufurd D, et al. 2002. Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. *J Neuropsychiatry Clin Neurosci*. 14:37–43. doi:10.1176/jnp.14.1.37

van Duijn E, Kingma EM, van der Mast RC. 2007. Psychopathology in verified Huntington's disease gene carriers. *J Neuropsychiatry Clin Neurosci*. 19:441–448. doi:10.1176/jnp.2007.19.4.441

van Duijn E, Reedeker N, Giltay EJ, et al. 2010. Correlates of apathy in Huntington's disease. *J Neuropsychiatry Clin Neurosci*. 22:287–294. doi:10.1176/jnp.2010.22.3.287

Vinther-Jensen T, Larsen IU, Hjermind LE, et al. 2014. A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. Published online July 17. *Orphanet J Rare Dis*. 9:114. doi:10.1186/s13023-014-0114-8

Vogel A, Stokholm J, Andreasen R, et al. 2018. Psychometric properties and reference data for Danish versions of Free and Cued Selective Reminding Test, Category Cued Memory Test and Logical Memory. *Scand J Psychol*. 59:496–502. doi:10.1111/sjop.12470

Vogel A, Stokholm J, Jørgensen K. 2020. Normative data for eight verbal fluency measures in older Danish adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 17:114–124. doi:10.1080/13825585.2019.1593935

Walker FO. 2007. Huntington's disease. *Lancet*. 369:218–228. doi:10.1016/S0140-6736(07)60111-1

MANUSCRIPT II

On the association between apathy and deficits of social cognition and executive functions in Huntington's Disease

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Research Article

On the association between apathy and deficits of social cognition and executive functions in Huntington's disease

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Abstract

Objective: To investigate if executive and social cognitive dysfunction was associated with apathy in a large cohort of Huntington's disease gene expansion carriers. **Method:** Eighty premanifest and motor-manifest Huntington's disease gene expansion carriers (Mini-Mental State Examination score ≥ 24 and Montreal Cognitive Assessment score ≥ 19) and thirty-two controls were examined with the Lille Apathy Rating Scale (LARS), a tailored and quantitative measure of apathy, and a comprehensive cognitive battery on executive functions and social cognition (emotion recognition, theory of mind and sarcasm detection), as well as general correlates like demographic variables, and neuropsychiatric and cognitive screening tests. **Results:** The motor-manifest Huntington's disease gene expansion carriers had significantly different scores on most measures of social cognition and executive functions, compared to premanifest and control participants. Apathy was significantly correlated with most executive test scores, but the Emotion Hexagon was the only social cognitive test score significantly correlated with apathy. We found that the motor score and the depression score were the only significant predictors of the apathy score, when the social cognitive and executive tests with the strongest association with the global LARS score were entered into a multiple stepwise regression model. No cognitive test score could significantly predict apathy. The model explained 21 % of the total variance. **Conclusion:** Despite being significantly correlated with apathy neuropsychological variables did not have a significant impact on apathy when variables as depression and motor symptoms were taken into account. Apathy should be considered an independent symptom of Huntington's disease that requires specific examination.

Keywords: apathy; Huntington's disease; social cognition; executive functions; cognitive function; emotion recognition

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Introduction

The manifestations of the autosomal dominant inherited neurodegenerative disease Huntington's disease (HD) include motor disturbances, neuropsychiatric symptoms, and cognitive dysfunction (McColgan & Tabrizi, 2018; Snowden, 2017). These cardinal symptoms are often accompanied by behavioral symptoms like apathy, irritability, perseverance, psychosis, and affective symptoms (Craufurd et al., 2001; Eddy et al., 2016). Apathy can be found in 34 % to 76 % of patients with HD and is a very distressing and burdensome neuropsychiatric symptom for the caregivers (Craufurd et al., 2001; van Duijn, Kingma & van der Mast, 2007). Apathy may be a marker of disease progression (Camacho et al., 2018; Thompson et al., 2012) and is continuously associated with cognitive impairments, motor symptoms, and depression (Hendel et al., 2021; Reedeker et al., 2011; van Duijn et al., 2010). Theoretically, apathy can be considered a deficit in goal-directed behavior caused by dysfunction of the prefrontal cortex-basal ganglia circuits (Levy & Dubois, 2006). The investigation of apathy involves a focus on the different cognitive processes implicated in goal-directed behavior such as selection of action based on evaluation of reward value and effort, planning and execution, outcome evaluation, and learning (Ernst & Paulus, 2005; Le Heron et al., 2018). Shared neural mechanisms may explain the association between processes of goal-directed behavior and symptoms of HD.

Apathy has been shown to be associated with executive dysfunction in HD (Andrews et al., 2020; Baudic et al., 2006; Reedeker et al., 2011; van Duijn et al., 2010). The specific aspects of executive functions that are associated with apathy have to our knowledge not been investigated, but in previous studies, tests on attention, working memory, set-shifting, fluency, and inhibition have been used.

Apathy may also be associated with social cognitive deficits since a significant association was found in two recent studies with premanifest and early manifest HD gene expansion carriers (Kempnich et al., 2018; Osborne-Crowley et al., 2019). Moreover, Ruff and Fehr (2014) illustrated that social decision making is based on similar neural processes as the value evaluations of non-social factors implicated in goal-directed behavior, and research into the neurobiological basis of apathy has increasingly focused on regions of the limbic loop, which is also thought to be relevant for the value evaluation processes (Le Heron et al., 2018; Levy &

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Dubois, 2006; Martínez-Horta et al., 2018). Accordingly, impairments of social cognition, as well as more classical processes in goal-directed behavior caused by dysfunction of the cortico-basal ganglia-thalamo-cortico circuits, may constitute the basis of apathy in HD. The previous studies on the association between apathy and social cognitive functions had some methodological weaknesses. One study included only 32 premanifest and manifest participants, and assessment of apathy was based on family ratings (Kempnich et al., 2018). In the study by Osborne-Crowley et al. (2019), the indirect associations were investigated based on a classification of patients as apathetic or nonapathetic. Thus, whether the association between apathy and social cognition is based on specific functions, like emotion recognition as in the previous studies, or if other functions contribute to this association is not known. Further, a more comprehensive examination of apathy could indicate if an association between apathy and social cognitive or executive functions is dependent on the degree or type of apathy.

In the present study, we aimed to investigate if executive and social cognitive dysfunction is associated with apathy (as measured by a tailored, quantitative rating scale) in a large group of HD gene expansion carriers. We analyzed if scores on the Lille Apathy Rating Scale (LARS; Sockeel et al., 2006) were associated with tasks of social cognition and executive functions when examined with a broad neuropsychological battery. By examining the associations between apathy and several executive and social cognitive tests, we wished to investigate to which degree the tests of each domain were associated with apathy and if different aspects of executive functions and social cognition were associated with apathy. Moreover, we examined the associations between apathy and variables as demographic information and results from neuropsychiatric measures. Finally, we examined which variables could significantly predict the degree of apathy, when both cognitive and basic clinical measures were also analyzed.

Methods

Participants

Eighty HD gene expansion carriers were included from the Neurogenetics Clinic, Danish Dementia Research Centre, Rigshospitalet, Copenhagen, Denmark, from June 2017 to June 2020. This cohort of participants have previously been described in Hendel et al. (2021).

Inclusion and exclusion criteria

The participants were included based on the following criteria; a Mini-Mental State Examination (MMSE) score ≥ 24 (Folstein et al., 1975), a Montreal Cognitive Assessment (MoCA) score ≥ 19 (Nasreddine et al., 2005), and a CAG repeat length ≥ 39. Exclusion criteria were other neurological disease, ongoing alcohol or drug abuse, or a native language other than Danish.

Classification of participants

Participants were classified as premanifest HD gene expansion carriers (N = 40) if their Unified Huntington's Disease Rating Scale-99 Total Motor score (UHDRS-TMS) (Huntington's Study Group, 1996) was ≤ 5, without substantial motor symptoms. If their UHDRS-TMS was > 5, they were given a classification of motor-manifest HD gene expansion carriers (N = 40).

Controls

The control group consisted of thirty-two previous 50 % at risk individuals tested negative for the gene expansion (with a CAG repeat length of < 30) before inclusion in this study. These individuals were chosen over unrelated healthy controls to better match for psychosocial and environmental factors.

All participants went through genetical counselling and were informed of their genetic status prior to and independently from study enrolment.

Procedure and instruments

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-17002606), and it was completed in accordance to the Helsinki Declaration. Informed consent was obtained from all participants before enrolment in the study. The participants had a minimum of two planned visits; in random order participants went through a neurological examination and a neuropsychological examination. In addition to the measures outlined above, the neurological examination also included neuropsychiatric screening tests, the Hamilton Depression Scale (HAM-17) (Hamilton, 1960), and the Symptom Checklist-90 Revised (SCL-90-R) (Derogatis, 2009). Measures of disease progression, the CAG repeat length and a CAP score, were also included in the study. The CAG repeat length represents an indirect measure of the amount of toxic huntingtin that the individual is exposed to. The CAP score was used as a measure of disease progression based on age and the CAG repeat length. Both the CAG repeat length and the CAP scores were used to examine the importance of disease progression for apathy. All examinations were performed by the same physician (MNNH) and neuropsychologist (RKH).

Apathy

Apathy was examined using the Lille Apathy Rating Scale (LARS), a standardized structured interview with 33 items divided into 9 domains based on main clinical manifestations of apathy (Sockeel et al., 2006). A global score is calculated as the sum of all items ranging from −36 to 36, with a higher score indicating more severe symptoms of apathy. Four subtypes describe the distinct dimensions of apathy; Intellectual Curiosity (decreased interest and perceived need for knowledge), Emotions (blunting of emotions and lack of concern), Action Initiation (decreased everyday productivity and lack of initiative), and Self Awareness (extinction of the awareness of self). Each of the four subtypes has an average score of −4 to 4. The results of the LARS have been presented previously in Hendel et al. (2021), but all other analyses are new for the current study.

Neuropsychological examination

The neuropsychological examination consisted of an extensive examination with a test-battery on premorbid level of intelligence, psychomotor speed and attention, memory, visuospatial functions, executive functions, and social cognition. Here, only the tests from the executive functions and social cognition are reported.

Executive functions

The executive functions were examined with the Symbol Digit Modality Test (SDMT), the Trail Making Test B (TMT B) (Reitan, 1955), the Stroop Test (100 words) (Stroop, 1935), the Brixton Test (Burgess & Shallice, 1997), the Lexical and Semantic Fluency Tests (Lezak et al., 2004), and an Alternating Fluency Test.

The Symbol Digit Modalities Test

The SDMT investigates psychomotor speed through a brief substitution test where participants with the use of a reference key pair nine different numbers with specific geometric symbols (Smith, 1982). Participants have 90 sec to pair as many numbers as possible. Number of correct responses was recorded and used for analysis.

The Trail Making Test B

The TMT B is a set-shifting test where participants should connect circles with the numbers 1–13 and the letters A-L, alternating between numbers and letters in an ascending sequence (Reitan, 1955). Time to completion was recorded.

The Stroop Interference Test

The Stroop Interference Test is a test of interference and inhibition. The 100 words version of the Stroop Interference Test consists of a simple reading task and an interference test (Stroop, 1935). In the interference test, participants are asked to name the color of the ink that the words are printed in. The words are names of colors that does not correspond to the color of the printed ink. For example, would the word red be printed in blue and the participants should say blue. Participants were instructed to complete the test as fast as possible. Time to completion was recorded for the interference test.

The Brixton Test

The Brixton Test measures task analysis and consists of a stimulus book where each page presents ten circles numbered 1–10 in the same basic display, but for each page one circle is printed blue (Burgess & Shallice, 1997). The participants must guess the pattern of the movement of the blue circle based on the positions from previous pages and from page to page indicate the position of the blue circle on the next page. No feedback is given during the test. The number of errors ($\leq$ 54) was recorded for analysis.

The Lexical Fluency Test

In the Lexical Fluency Test, participants must name as many words as possible within one minute beginning with each of the letters F, A, and S (Lezak et al., 2004). All Danish words were accepted, except for proper nouns. The number of words was recorded and summed for a total score.

The Semantic Fluency Test

In the Semantic Fluency test, participants must name as many animals as possible within one minute. All types or categories of animals were accepted, and specific animals within a named category were also accepted. The total number of animals was recorded.

The Alternating Fluency Test

The Alternating Fluency Test measures internal attentional control. Participants must name as many words as possible within one minute, beginning with the letter K and the letter B in an alternating order. All words were accepted except proper nouns. Improper alternations were recorded as incorrect. The number of words in correct alternating order was recorded for analysis.

Social cognition

The social cognitive tasks consisted of The Awareness of Social Inference Test (TASIT) (McDonald et al., 2003), the Emotion Hexagon (EH) (Calder et al., 1996; Sprengelmeyer et al., 1996), and Reading the Mind in the Eyes Test – revised version (RMET) (Baron-Cohen et al., 2001).

The Awareness of Social Inference Test

The Danish version of The Awareness of Social Inference Test (TASIT) Social Inference Minimal (SI-M) Test consists of 15 short videotaped vignettes (15–53 s) portraying everyday conversational exchanges between two persons (Bliksted et al., 2014). Of the 15 vignettes, five depicts *sincere* exchanges and 10 depicts sarcastic exchanges. The sarcastic vignettes are either portraying *simple sarcasm* (five vignettes), where the words are incongruent with the paralinguistic and facial cues, or *paradoxical sarcasm* (five vignettes), where the dialogue is meaningless unless it is understood that the person is being sarcastic. Outcomes are SI-M total score (0–60) and three subscores; the *sincere* score (0–20), the *simple sarcasm* score (0–20), and the *paradoxical sarcasm* score (0–20).

The Emotion Hexagon Test

The Emotion Hexagon Test (EH) consists of 30 pictures of facial expression of six basic emotions; happiness, surprise, fear, sadness, anger, and disgust (Calder et al., 1996; Sprengelmeyer et al., 1996). The pictures are morphed along a spectrum, so that each emotion is blended with two neighboring emotions (e.g., happiness is morphed with surprise and anger; the ratio of the happiness-surprise spectrum is 90:10, 70:30, 50:50, 30:70, and 10:90). Emotions blended by 50% served as neutral stimuli and were not included in the final score. Before the presentation of the pictures, the participants were shown a card with the names of the six emotions, and each emotion was explained. This card was present during the entire test. The pictures were presented in a random order and a total score (0–24) represents the number of correct answers.

The Reading the Mind in the Eyes Test

The revised version of the Reading the Mind in the Eyes Test (RMET) comprises 36 pictures of the eye region of different persons (male and female), depicting various negative and positive emotional states (Baron-Cohen et al., 2001). Each picture was presented together with four words describing a possible emotional state. The participants were presented to a wordlist of all possible words, explained and used in a sentence, and were encouraged to look at it, if they felt uncertain about the meaning of a word. The participants were then asked to choose the word from the four possibilities that best described the mental state of the portraited person. A total score (0–36) indicates the number of correct responses.

Statistical analyses

Group comparisons were performed with analysis of variance (ANOVA) or Kruskal-Wallis (when assumptions of homogeneity of variance were not met). Dunnett's t-tests or Mann-Whitney U tests (for skewed distributions) were used for *post hoc* comparisons. Effect sizes were calculated as $\hat{d} = \frac{\bar{x}_1 - \bar{x}_2}{s}$ for the Dunnett's t-tests, and based on the formula by (Field, 2018): $r = \frac{z}{\sqrt{N}}$ for the Mann-Whitney U tests. The Bonferroni–Holm correction was applied to adjust the level of significance on all analyses with multiple

Table 1. Demographic data and results from the cognitive and neuropsychiatric screening tests for the HD gene expansion carriers and the controls. Results are presented as mean (SD)

	HD Gene Expansion Carriers		
	Motor-Manifest	Premanifest	Controls
N	40	40	32
Age (years)	51.7 (11.9)‡	41.3 (11.0)	48.1 (14.1)
Sex (M/F)	21/19	24/16	13/19
UHDRS-TMS	23.3 (13.5)* ‡	1.5 (1.5)	1.3 (1.3)
CAG Repeat Length	42.8 (2.5)*	41.8 (2.4)*	19.8 (4.0)
CAP Score	359.7 (92.0)‡	248.7 (80.3)	–
HAM-17 Score	4.3 (3.6)‡	2.5 (3.1)	2.7 (3.0)
SCL-90-R GSI Score	51.1 (12.4)* ‡	42.0 (10.1)	43.7 (11.2)

Note. * Statistically significant difference from the controls ($p < .05$). ‡ Statistically significant difference from the premanifest HD ($p < .05$).
HD: Huntington's disease; SD: standard deviation; UHDRS: Unified Huntington's Disease Rating Scale. TMS: Total Motor Score. CAG: cytosine-adenine-guanine; CAP: cytosine-adenine-guanine age product; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; HAM-17: Hamilton Depression Scale; SCL-90-R: Symptom Checklist-90 Revised.

comparisons. For all HD gene expansion carriers, a CAP score was calculated as $CAP = Age \cdot (CAG - 35.5)$ based on Penney et al. (1997). For the total group of HD gene expansion carriers, association analyses were performed between the LARS and social cognitive and executive tasks. No transformation of data was performed, and negative values of the LARS remained negative in the analyses. Correlation analyses were applied, and Pearson's *r* or Spearman's *rho* (for skewed distributions) was used to assess the level of significance. Based on the results from Hendel et al. (2021), we entered the UHDRS-TMS and the HAM-17 score into a multiple stepwise regression analysis with the global LARS as dependent variable, along with one social cognitive test and one test of executive function. We entered the social cognitive and executive tests with the strongest association with the global LARS score, based on the correlation coefficients. Plot of residuals was used for model control for the regression analysis.

The alpha-level for significance was 5% for all analyses.

Results

Differences between HD gene expansion carriers and controls

Demographic data and the results on the cognitive and neuropsychiatric screening tests are presented in Table 1. Significant differences were found between the motor-manifest HD gene expansion carriers and the premanifest HD gene expansion carriers and the controls on almost all measures. The motor-manifest HD gene expansion carriers were significantly older than the premanifest HD gene expansion carriers, but there was no difference in the distribution of sex between the groups. Measures of disease progression (UHDRS-TMS and CAP score) were significantly higher in the motor-manifest HD gene expansion carriers, when compared to both premanifest HD gene expansion carriers and controls. Both the premanifest and the motor-manifest HD gene expansion carriers had higher CAG repeat length than the controls. Concerning the neuropsychiatric tests (HAM-17 and SCL-90-R GSI), the motor-manifest HD gene expansion carriers scored significantly higher than the two other groups.

Table 2 presents the results on the LARS and the social cognitive and executive tasks for the HD gene expansion carriers and the controls. When compared to the premanifest HD gene expansion carriers and controls, the motor-manifest HD gene expansion carriers had significantly higher scores on the global LARS ($p = .009$, $p = .001$, respectively) and on the subscales Intellectual Curiosity ($p = .044$, $p = .004$ respectively) and Action Initiation (both $p < .001$). However, when correcting for multiple comparisons, the difference between the premanifest and motor-manifest HD gene expansion carriers on the Intellectual Curiosity subscale could not be considered significant. On the social cognitive and executive tasks, the motor-manifest HD gene expansion carriers had significant different scores on most measures (except on the TASIT subscores), when compared to the premanifest HD gene expansion carriers and the controls. The largest effect sizes were found for TMT B (premanifest: $r = .67$, controls: $r = -.65$) and Stroop Interference Test score (premanifest: $r = .54$, controls: $r = -.55$). There were no significant differences between the premanifest HD gene expansion carriers and the controls on the social cognitive or executive tests.

Associations between apathy and cognitive tests

The association analyses between the global LARS and social cognitive and executive tasks for the total group of HD gene expansion carriers are presented in Table 3. The only significant correlation between apathy and the social cognitive tests was a negative association between the EH total score and the global LARS score (rho = −.27, p = .014), indicating that individuals with a high degree of apathy scored lower on the EH test. No other significant correlations were found between apathy on the global LARS and social cognitive test scores. Scores on almost all executive tests (except the Stroop Test interference score and the Brixton Test score) were significantly negatively correlated with the global LARS score, indicating that a higher degree of apathy is associated with lower performance on the executive tests.

Associations between apathy and demographic variables

When assessing the associations between scores on the LARS and the demographic variables, we found a significant correlation between the UHDRS-TMS and the global LARS score (*rho* = .35, $p = .002$). Also, the global LARS score was significantly correlated with the neuropsychiatric screening tests (HAM-17: *rho* = .40, $p < .001$; SCL-90-R GSI: $r = .30$, $p = .008$).

Variables explaining apathy in HD gene expansion carriers

A multiple regression analysis was performed to examine which variables could explain the degree of apathy in the total group of HD gene expansion carriers. The analysis included the global LARS score as outcome variable and the UHDRS-TMS, the HAM-17 score, the EH test, and the Semantic Fluency test as predictor variables. When the predictor variables were entered the model, we found that the UHDRS-TMS ($b = 0.14$, $SE_b = 0.05$, $CI = [0.05; 0.23]$, $p = .003$) and the HAM-17 score ($b = 0.41$, $SE_b = 0.19$, $CI = [0.03; 0.79]$, $p = .034$) could significantly predict the global LARS score (*constant* = –26.32, $SE_c = 0.94$, $CI = [-28.19; -24.45]$, $p = <.001$). This model could explain 21 % of the total variance ($R^2 = .21$, $p < .001$). Neither the social cognitive test nor the executive test was entered the final model. Thus, the burden of depressive symptoms and the motor symptoms had a significant association with apathy symptoms, but executive symptoms and social cognitive symptoms did not have additional impact on the global LARS score.

Table 2. Results on the Lille Apathy Rating Scale, the social cognitive tasks, and the executive tasks for the HD gene expansion carriers and controls. Results are presented as mean (SD)

	HD Gene Expansion Carriers		
	Motor-Manifest	Premanifest	Controls
N	40	40	32
Apathy			
LARS Global Score	−21.2 (6.9)* ‡	−25.2 (4.3)	−26.3 (3.0)
Intellectual Curiosity Score	−2.4 (0.9)*	−2.8 (0.7)	−2.9 (0.5)
Emotions Score	−2.3 (1.0)	−2.6 (1.0)	−2.6 (0.7)
Action Initiation Score	−2.4 (1.1)* ‡	−3.4 (0.7)	−3.5 (0.6)
Self-Awareness Score	−2.4 (1.6)	−2.1 (1.8)	−2.5 (1.5)
Social Cognition			
TASIT SI-M Total Score	48.4 (5.2)* ‡	52.4 (3.4)	52.5 (4.5)
Sincere Score	14.5 (3.7)	16.0 (2.7)	15.9 (3.2)
Simple Sarcasm Score	15.8 (3.3)	17.2 (2.2)	17.4 (2.4)
Paradoxical Sarcasm Score	18.2 (2.5)	19.1 (1.1)	19.3 (1.2)
EH Total Score	16.1 (4.6)* ‡	19.5 (2.3)	20.1 (2.6)
RMET Total Score	20.9 (5.1)* ‡	25.6 (3.1)	25.0 (3.6)
Executive Functions			
SDMT Total Score	34.6 (12.3)* ‡	54.2 (11.2)	57.7 (11.6)
TMT B (sec)	95.3 (51.4)* ‡	44.1 (17.5)	44.3 (14.2)
Lexical Fluency Score (FAS)	31.0 (12.6)* ‡	44.9 (10.2)	46.0 (12.8)
Semantic Fluency Score (Animals)	16.7 (5.7)* ‡	23.8 (4.3)	25.4 (5.3)
Alternating Fluency Score (K-B)	10.5 (4.2)* ‡	15.5 (3.2)	15.1 (4.0)
Stroop Test Incongruence Score (sec)	164.0 (59.2)* ‡	106.4 (22.7)	102.3 (21.4)
Brixton Test Score	16.8 (8.6) ‡	12.3 (5.6)	13.8 (7.0)

Note. * Statistically significant difference from the controls ($p < .05$). ‡ Statistically significant difference from the premanifest HD ($p < .05$).
HD: Huntington's disease; SD: standard deviation; LARS: The Lille Apathy Rating Scale; TASIT: The Awareness of Social Inference Test; SI-M: Social Inference Minimal; EH: Emotion Hexagon; RMET: Reading the Mind in the Eyes Test; SDMT: Symbol Digit Modality Test; TMT B: Trail Making Test B.

Table 3. Correlations between scores on the LARS and the social cognitive and executive tasks for the total group of HD gene expansion carriers.

	Global LARS Score
Social Cognition	
TASIT SI-M Total Score	−.14
Sincere Score	−.13
Simple Sarcasm Score	−.02
Paradoxical Sarcasm Score	−.07
EH Total Score	*−.27**
RMET Total Score	−.20
Executive Functions	
SDMT Total Score	*−.33**
TMT B (sec)	*.28**
Lexical Fluency Score	*−.27**
Semantic Fluency Score	*−.35**
Alternating Fluency Score	*−.27**
Stroop Test Incongruence Score (sec)	.19
Brixton Test Score	.19

Note. *Statistically significant ($p < .05$).
HD: Huntington's disease; LARS: The Lille Apathy Rating Scale; TASIT: The Awareness of Social Inference test; SI-M: Social Inference Minimal; EH: Emotion Hexagon; RMET: Reading the Mind in the Eyes Test; SDMT: Symbol Digit Modality Test; TMT B: Trail Making Test B.

Discussion

We investigated the association between apathy, as measured by a tailored quantitative rating scale, and social cognitive and executive dysfunction. In a cohort of 80 premanifest and motor-manifest HD gene expansion carriers, examined with a comprehensive battery investigating both executive functions and social cognitive processes (emotion recognition, theory of mind, and sarcasm detection), we found significant correlations between most executive test performance and the apathy score on the global LARS. Despite being significantly reduced in motor-manifest HD gene expansion carriers, most social cognitive test performances were not associated with apathy. Only the EH test score was significantly correlated with the global LARS. This result was in accordance to previous studies but unlike previous studies, we also examined if executive dysfunctions or social cognitive impairments could be predictive of apathy. Such finding would help explain the development of apathy and indicate if cognitive test performance could be used to support a clinical assessment of apathy. However, when entering the executive and social cognitive variables with the highest correlation coefficient, neither the Semantic Fluency test nor the EH test could predict the apathy score on the global LARS, when more general variables were added to the model.

Our results support the results of previous studies, where executive dysfunction has been linked to apathy both in HD (Andrews et al., 2020; Baudic et al., 2006; Reedeker et al., 2011; van Duijn et al., 2010) and in other neurodegenerative diseases like Parkinson's disease (Dujardin et al., 2009; Pluck & Brown, 2002) and Alzheimer's disease (McPherson et al., 2002). As expected, most executive test performances were significantly impaired in motor-manifest HD gene expansion carriers, compared to premanifest HD gene expansion carriers and controls. But unlike previous studies (Baake et al., 2017; Duff et al., 2010; Larsen et al., 2015; Paulsen et al., 2013), premanifest HD gene expansion carriers were not impaired on any tests of psychomotor speed or other executive functions. We found that several executive test scores were significantly correlated to the global LARS score when examining the entire group of HD gene expansion carriers. Interestingly, the tests that were significantly associated with apathy were the same as used in previous studies (Andrews et al., 2020; Baudic et al., 2006; Reedeker et al., 2011; van Duijn et al., 2010) and included functions like attentional control, set-shifting, psychomotor speed, and fluency. However, the results could not demonstrate if any aspect of the executive functions were more associated to apathy than others, as the correlations coefficients were of almost equal sizes. It can be hypothesized that apathy affects the executive

functions of HD gene expansion carriers, as apathy can lead to an inhibition of action. The inhibition of action could affect the executive functions by reducing the psychomotor speed or the ability to perform well on fluency tests by causing inactivity. However, as the present study did not examine the direction of the association, this cause of effects is only hypothetical. Yet, our study did examine if executive dysfunction could be used as a predictor of apathy. Interestingly, when entering the semantic fluency test (the executive test with the highest correlation coefficient) as a predictor variable in the multiple stepwise regression model, we did not show such predictive capabilities. This was a surprising finding which underline the importance of a deeper investigation of the associations between apathy and executive functions, as the association could be driven by other factors not included in this study.

In two previous studies, it has been shown that emotion recognition may be linked to apathy in premanifest and manifest HD (Kempnich et al., 2018; Osborne-Crowley et al., 2019) which we sought to replicate. Also, we extended the examination to involve several social cognitive functions. In accordance with previous studies (Allain et al., 2011; Bora, Velakoulis & Walterfang, 2016; Eddy et al., 2018; Larsen et al., 2016; Philpott et al., 2016), we showed that social cognitive test scores were significantly impaired in motor-manifest HD gene expansion carriers. In contrast, we showed that only the emotion recognition performance on the EH test was significantly correlated to apathy on the global LARS. The remaining social cognitive test performances were not significantly correlated with the apathy score. While the EH is an emotion recognition task, the RMET and the TASIT are both tests of theory of mind, which might not be associated with apathy. One explanation for why the RMET task was not associated with apathy in this study could be that while the task draws on abilities of both emotion recognition and theory of mind, it is directed at examining theory of mind. These results are in accordance with the previous studies (Kempnich et al., 2018; Osborne-Crowley et al., 2019), and similar findings have been shown in Parkinson's disease (Martínez-Corral et al., 2010; Robert et al., 2014). Thus, although social cognition as a domain might not be associated with apathy, processes of emotion recognition might be to some extent. One explanation for this association is that apathy reduces the social value evaluation of emotions and thus affects the goal-directed decision making when presented with facial stimuli (Ruff & Fehr, 2014).

This study widened the investigation of the association between apathy and social cognitive and executive dysfunction by examining the predictive capabilities of these cognitive functions. To our knowledge, this is the largest study to include social cognitive functions as a predictor of apathy. Our results suggest that apathy is correlated to variables of general progression on all three cardinal symptoms of HD and illustrate that apathy is a marker of disease progression. When we entered the UHDRS-TMS, the HAM-17 score, the EH test, and the Semantic Fluency test into a multiple stepwise regression model with the global LARS score as the dependent variable, we found that the UHDRS-TMS and the HAM-17 score were the only predictive variables of the global LARS score. This was in line with studies showing that apathy is closely associated with disease progression and depressive symptoms (Camacho et al., 2018; Hendel et al., 2021; Reedeker et al., 2011; Thompson et al., 2012; van Duijn et al., 2010). Despite being significantly correlated with the global LARS score, the EH test score was not a significant predictor of apathy in our study. This contrasts with the Kempnich et al. (2018) study and suggests that the significant correlation between emotion recognition and apathy might be a result of co-occurrence because of shared underlying neuropathology, or because both symptoms are dependent on a third explainable variable. In this instance, the disease progression could be one explanation for the progression of both symptoms. Accordingly, the UHDRS-TMS as a proxy for disease progression was a significant predictor of the global LARS score in our final stepwise multiple regression model. However, this model only explained 21% of the total variance and thus other factors must also be affecting the prediction of apathy. Among possible explainable factors are age, the male sex, or the use of pharmacological treatment like neuroleptics or benzodiazepines (van Duijn et al., 2010). None of these factors were included in the analyses of the present study.

Limitations and future directions

One important limitation of the present study that need mentioning concerns the self-reported nature of the LARS. While LARS is a sound and comprehensive measure of apathy, the participants must be able to recognize and acknowledge their perceived symptoms of apathy for the LARS to be a valid instrument. As HD gene expansion carriers have been found to have decreased insight into their own inabilities (McCusker & Loy, 2014), and since impaired awareness of deficits and apathy are both related to dysfunction of the frontal-subcortical circuitry (Duff et al., 2010), this could have affected the results. However, in recent studies, HD gene expansion carriers in early stages of the disease have been reported to be aware of their degree of apathy (Atkins et al., 2021; Baake et al., 2018) and since the present study included HD gene expansion carriers in the early stages of the disease, we do not believe that the results have been distorted by this to a large degree. However, future studies should seek to examine the awareness of deficits in HD gene expansion carriers, when investigating apathy.

Moreover, as this study included HD gene expansion carriers in premanifest or early stages of disease, we did not control for any possible pharmacological treatment that the participants might receive. However, as the participants were in early stages of disease, we would not expect them to receive treatment that could have affected the examination of their apathy symptoms, to a large degree. However, as treatment with neuroleptics and benzodiazepines might be associated with apathy (van Duijn et al., 2010), future studies should control for pharmacological treatment when examining apathy.

Conclusion

In conclusion, our results suggest that the examination of apathy in HD cannot be derived from the individual's performance on neuropsychological tests. That is, the present results do not support the hypothesis that apathy can be explained by dysfunction of the different cognitive processes implicated in goal-directed behavior, since the social cognitive and executive tests were not predictive of apathy. Instead, this study demonstrates that apathy should be seen as an independent symptom of HD that requires separate and specific examination by a comprehensive measure.

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Conflicts of interest. The authors declare that they have nothing to report.

References

Allain, P., Havet-Thomassin, V., Verny, C., Gohier, B., Lancelot, C., Besnard, J., Fasotti, L., & Le Gall, D. (2011). Evidence for deficits on different components of theory of mind in Huntington's disease. *Neuropsychology*, *25*(6), 741–751. https://doi.org/10.1037/a0024408

Andrews, S. C., Langbehn, D. R., Craufurd, D., Durr, A., Leavitt, B. R., Roos, R. A., Tabrizi, S. J., & Stout, J. C. (2020). Apathy predicts rate of cognitive decline over 24 months in premanifest Huntington's disease. *Psychological Medicine*, 1–7. https://doi.org/10.1017/S0033291720000094

Atkins, K. J., Andrews, S. C., Chong, T. T. J., & Stout, J. C. (2021). Multidimensional apathy: the utility of the dimensional apathy scale in Huntington's disease. *Movement Disorders Clinical Practice*, *8*(3), 361–370. https://doi.org/10.1002/mdc3.13147

Baake, V., Reijntjes, R. H. A. M., Dumas, E. M., Thompson, J. C., Roos, R. A. C., Bentivoglio, A. R., Biunno, I., Bronzova, J., Dunnett, S. B., Frich, J., Giuliano, J., Illarioshkin, S., Illmann, T., Klempír, J., Landwehrmeyer, G. B., Levey, J., McLean, T., Nielsen, J. E., Päivärinta, M., Pica, E. (2017). Cognitive decline in Huntington's disease expansion gene carriers. *Cortex*, *95*, 51–62. https://doi.org/10.1016/j.cortex.2017.07.017

Baake, V., van Duijn, E., & Roos, R. A. C. (2018). Huntington's disease gene expansion carriers are aware of their degree of apathy. *Journal of Neuropsychiatry and Clinical Neurosciences*, *30*(3), 183–187. https://doi.org/10.1176/appi.neuropsych.18020031

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *42*(2), 241–251. https://doi.org/10.1017/S0021963001006643

Baudic, S., Maison, P., Dolbeau, G., Boissé, M. F., Bartolomeo, P., Barba, G. D., Traykov, L., & Bachoud-Levi, A. C. (2006). Cognitive impairment related to apathy in early Huntington's disease. *Dementia and Geriatric Cognitive Disorders*, *21*(5–6), 316–321. https://doi.org/10.1159/000091523

Bliksted, V., Fagerlund, B., Weed, E., Frith, C., & Videbech, P. (2014). Social cognition and neurocognitive deficits in first-episode schizophrenia. *Schizophrenia Research*, *153*(1–3), 9–17. https://doi.org/10.1016/j.schres.2014.01.010

Bora, E., Velakoulis, D., & Walterfang, M. (2016). Social cognition in Huntington's disease: A meta-analysis. *Behavioural Brain Research*, *297*, 131–140. https://doi.org/10.1016/j.bbr.2015.10.001

Burgess, P. W., & Shallice, T. (1997). *The Hayling and Brixton tests*. Pearson Assessment.

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial Emotion Recognition after Bilateral Amygdala Damage: Differentially Severe Impairment of Fear. *Cognitive Neuropsychology*, *13*(5), 699–745. https://doi.org/10.1080/026432996381890

Camacho, M., Barker, R. A., & Mason, S. L. (2018). Apathy in Huntington's disease: A review of the current conceptualization. *Journal of Alzheimer's Disease & Parkinsonism*, *08*(02), 1–9. https://doi.org/10.4172/2161-0460.1000431

Craufurd, D., Thompson, J. C., & Snowden, J. S. (2001). Behavioral changes in Huntington disease. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, *14*(4), 219–226. https://doi.org/10.1097/WNN.0000000000000147

Derogatis, L. R. (2009). *SCL-90-R, Vejledning til administration og scoring, Dansk Version* (L. R. Derogatis (ed.)). Pearson.

Duff, K., Paulsen, J., Mills, J., Beglinger, L. J., Moser, D. J., Smith, M. M., Langbehn, D., Stout, J., Queller, S., & Harrington, D. L. (2010). Mild cognitive impairment in prediagnosed Huntington disease. *Neurology*, *75*(6), 500–507. https://doi.org/10.1212/WNL.0b013e3181eccfa2

Dujardin, K., Sockeel, P., Delliaux, M., Destée, A., & Defebvre, L. (2009). Apathy may herald cognitive decline and dementia in Parkinson's disease. *Movement Disorders*, *24*(16), 2391–2397. https://doi.org/10.1002/mds.22843

Eddy, C. M., Parkinson, E. G., & Rickards, H. E. (2016). Changes in mental state and behaviour in Huntington's disease. *The Lancet Psychiatry*, *3*(11), 1079–1086. https://doi.org/10.1016/S2215-0366(16)30144-4

Eddy, C. M., Rickards, H. E., & Hansen, P. C. (2018). Through your eyes or mine? The neural correlates of mental state recognition in Huntington's disease. *Human Brain Mapping*, *39*(3), 1354–1366. https://doi.org/10.1002/hbm.23923

Ernst, M., & Paulus, M. P. (2005). Neurobiology of decision making: A selective review from a neurocognitive and clinical perspective. *Biological Psychiatry*, *58*(8), 597–604. https://doi.org/10.1016/j.biopsych.2005.06.004

Field, A. (2018). Non-parametric models. In A. Field (Ed.), *Discovering statistics using IBM SPSS statistics* (5th ed., pp. 281–332). SAGE Publications.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198. https://doi.org/10.3744/snak.2003.40.2.021

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery and Psychiatry*, *23*, 56–62. https://doi.org/10.1192/bjp.bp.107.040485

Hendel, R. K., Hellem, M. N. N., Hjermind, L. E., Nielsen, J. E., & Vogel, A. (2021). Intellectual Curiosity and Action Initiation are Subtypes of Apathy Affected in Huntington Disease Gene Expansion Carriers. *Cognitive and Behavioral Neurology*, *34*(4), 295–302.

Huntington's Study Group. (1996). Unified Huntington's disease rating scale: Reliability and consistency. *Movement Disorders*, *11*(2), 136–142.

Kempnich, C. L., Andrews, S. C., Fisher, F., Wong, D., Georgiou-Karistianis, N., & Stout, J. C. (2018). Emotion recognition correlates with social-neuropsychiatric dysfunction in Huntington's disease. *Journal of the International Neuropsychological Society*, *24*(5), 417–423. https://doi.org/10.1017/S1355617717001308

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2015). Assessing impairment of executive function and psychomotor speed in premanifest and manifest Huntington's disease gene-expansion carriers. *Journal of the International Neuropsychological Society*, *21*(3), 193–202. https://doi.org/10.1017/S1355617715000090

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2016). Do i misconstrue? Sarcasm detection, emotion recognition, and theory of mind in Huntington disease. *Neuropsychology*, *30*(2), 181–189. https://doi.org/10.1037/neu0000224

Le Heron, C., Apps, M. A. J., & Husain, M. (2018). The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia*, *118*(2017), 54–67. https://doi.org/10.1016/j.neuropsychologia.2017.07.003

Levy, R., & Dubois, B. (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cerebral Cortex*, *16*(7), 916–928. https://doi.org/10.1093/cercor/bhj043

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). Verbal functions and language skills. In M. D. Lezak, D. B. Howieson, & D. W. Loring (Eds.), *Neuropsychological assessment* (4th ed., pp. 501–530). Oxford University Press.

Martínez-Corral, M., Pagonabarraga, J., Llebaria, G., Pascual-Sedano, B., García-Sánchez, C., Gironell, A., & Kulisevsky, J. (2010). Facial emotion recognition impairment in patients with Parkinson's disease and isolated apathy. *Parkinson's Disease*, *2010*. https://doi.org/10.4061/2010/930627

Martínez-Horta, S., Perez-Perez, J., Sampedro, F., Pagonabarraga, J., Horta-Barba, A., Carceller-Sindreu, M., Gomez-Anson, B., Lozano-Martinez, G. A., Lopez-Mora, D. A., Camacho, V., Fernández-León, A., Carrió, I., & Kulisevsky, J. (2018). Structural and metabolic brain correlates of apathy in Huntington's disease. *Movement Disorders*, *33*(7), 1151–1159. https://doi.org/10.1002/mds.27395

McColgan, P., & Tabrizi, S. J. (2018). Huntington's disease: A clinical review. *European Journal of Neurology*, *25*(1), 24–34. https://doi.org/10.1111/ene.13413

McCusker, E., & Loy, C. T. (2014). The many facets of unawareness in Huntington disease. *Tremor and Other Hyperkinetic Movements*, *2014*(1), 1–8. https://doi.org/10.7916/D8FJ2FD3

McDonald, S., Flanagan, S., Rollins, J., & Kinch, J. (2003). A new clinical tool for assessing social perception after traumatic brain injury. *Journal of Head Trauma Rehabilitation*, *18*(3), 219–238.

McPherson, S., Fairbanks, L., Tiken, S., Cummings, J. L., & Back-Madruga, C. (2002). Apathy and executive function in Alzheimer's disease. *Journal of the International Neuropsychological Society*, *8*(3), 373–381. https://doi.org/10.1017/S1355617702813182

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. *Journal of American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221

Osborne-Crowley, K., Andrews, S. C., Labuschagne, I., Nair, A., Scahill, R., Craufurd, D., Tabrizi, S. J., & Stout, J. C. (2019). Apathy associated with impaired recognition of happy facial expressions in Huntington's disease. *Journal of the International Neuropsychological Society*, *25*(5), 453–461. https://doi.org/10.1017/S1355617718001224

Paulsen, J. S., Smith, M. M., & Long, J. D. (2013). Cognitive decline in prodromal Huntington disease: Implications for clinical trials. *Journal of Neurology, Neurosurgery and Psychiatry*, *84*(11), 1233–1239. https://doi.org/10.1136/jnnp-2013-305114

Penney, J. B., Vonsattel, J.-P., MacDonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease. *Annals of Neurology*, *41*, 689–692.

Philpott, A. L., Andrews, S. C., Staios, M., Churchyard, A., & Fisher, F. (2016). Emotion evaluation and social inference impairments in Huntington's disease. *Journal of Huntington's Disease*, *5*(2), 175–183. https://doi.org/10.3233/JHD-160190

Pluck, G. C., & Brown, R. G. (2002). Apathy in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *73*, 636–642.

Reedeker, N., Bouwens, J. A., van Duijn, E., Giltay, E. J., Roos, R. A. C., & van der Mast, R. C. (2011). Incidence, course, and predictors of apathy in Huntington's disease: A two-year prospective study. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*, 434–441. https://doi.org/10.1176/appi.neuropsych.23.4.434

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting Psychology*, *19*(5), 393–394. https://doi.org/10.1037/h0044509

Robert, G., Le Jeune, F., Dondaine, T., Drapier, S., Péron, J., Lozachmeur, C., Sauleau, P., Houvenaghel, J. F., Travers, D., Millet, B., Vérin, M., & Drapier, D. (2014). Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: A PET study with conjunction analyses. *Journal of Neurology, Neurosurgery and Psychiatry*, *85*(10), 1153–1158. https://doi.org/10.1136/jnnp-2013-307025

Ruff, C. C., & Fehr, E. (2014). The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience*, *15*(8), 549–562. https://doi.org/10.1038/nrn3776

Salehinejad, M. A., Ghanavati, E., Rashid, M. H. A., & Nitsche, M. A. (2021). Hot and cold executive functions in the brain: A prefrontal-cingular network. *Brain and Neuroscience Advances*, *5*, 239821282110077. https://doi.org/10.1177/23982128211007769

Smith, A. (1982). *Symbol digit modalities test: manual*. Western Psychological Services.

Snowden, J. S. (2017). The neuropsychology of Huntington's disease. *Archives of Clinical Neuropsychology*, *32*(7). https://doi.org/10.1093/arclin/acx086

Sockeel, P., Dujardin, K., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS): A new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *77*(5), 579–584. https://doi.org/10.1136/jnnp.2005.075929

Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H., Hömberg, V., Perrett, D. I., & Rowland, D. (1996). Loss of disgust: Perception of faces and emotions in Huntington's disease. *Brain*, *119*(5), 1647–1665. https://doi.org/10.1093/brain/119.5.1647

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Thompson, J. C., Harris, J., Sollom, A. C., Stopford, C. L., Howard, E., Snowden, J. S., & Craufurd, D. (2012). Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *24*(1), 53–60. https://doi.org/10.1176/appi.neuropsych.11030057

Tsermentseli, S., & Poland, S. (2016). Cool versus hot executive function: A new approach to executive function. *Encephalos*, *53*(1), 11–14.

van Duijn, E., Kingma, E. M., & van der Mast, R. C. (2007). Psychopathology in verified Huntington's disease gene carriers. *Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(4), 441–448. https://doi.org/10.1176/jnp.2007.19.4.441

van Duijn, E., Reedeker, N., Giltay, E. J., Roos, R. A. C., & van der Mast, R. C. (2010). Correlates of apathy in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(3), 287–294. https://doi.org/10.1176/jnp.2010.22.3.287

MANUSCRIPT III

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Impairments of social cognition significantly predict the progression of functional decline in Huntington's disease: A 6-year follow-up study

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ABSTRACT

This study sought to investigate if there was a significant difference between the Huntington's Disease gene expansion carriers who were impaired on the cognitive domains, *social cognition* and *executive functions*. Also, it was investigated which of the cognitive domains could predict the decrease in total functional capacity over a 6-year follow-up period. Premanifest and motor-manifest Huntington's Disease gene expansion carriers ($N = 98$), were examined with a neurological and neuropsychological examination at Time 1 (year 2012–2013). Regression-based normative data was used to classify impairments on the two cognitive domains. Follow-up participants ($N = 80$) had their functional capacity reexamined at Time 2 (year 2018–2020), to examine which cognitive domain could predict the decrease in functional capacity over the 6-year follow-up. More than 50% of the participants were impaired on the domain of *social cognition*. These participants were significantly different from the participants who were impaired on *executive functions*. The motor function and impairments on *social cognition* significantly predicted the decline in functional capacity. The Emotion Hexagon test was the only significant social cognitive task, that predicted the decline in functional capacity. Social cognition includes unique and separate functions in Huntington's Disease, unaffected by executive functions. This study emphasizes the importance of regular assessment of social cognition in Huntington's Disease and the clinical relevance of impaired social cognitive function.

KEYWORDS

Emotion recognition; executive function; Huntington's Disease; social cognition; total functional capacity

Introduction

The autosomal dominantly inherited neurodegenerative disease, Huntington's Disease (HD), is caused by an expansion of the Cytosine-Adenine-Guanine (CAG) trinucleotide repeat in the huntingtin gene on chromosome 4 (McColgan & Tabrizi, 2018). The clinically evident symptoms of HD include motor symptoms, cognitive impairments, and psychiatric symptoms. Despite wide variation, the formal onset of HD is most often in mid-age, and the diagnosis is based on the motor symptoms and signs, combined with a positive gene test (Paulsen, 2011; Walker, 2007). However, in many cases, cognitive impairments and psychiatric symptoms precede the motor disturbances and formal diagnosis of HD up to 15 years before (Paulsen, 2011; Paulsen et al., 2008; Snowden, 2017; Vinther-Jensen et al., 2014). These symptoms lead to a decline in the functional capacity of individuals with HD, a capacity which describes the functional status and "self-care" capacities of individuals with HD (Beglinger et al., 2010). There is a robust evidence base for the course of the cognitive impairments in HD, with primary impairments found in psychomotor speed, attention, and executive functions in premanifest HD, followed by a decline in memory and visuospatial function in more advanced stages of disease (Paulsen, 2011; Snowden, 2017). Cognitive symptoms, specifically executive dysfunction and impaired psychomotor speed, have been found to significantly predict the functional decline in the daily living of patients with HD (Eddy & Rickards, 2015a). Likewise, neuropsychiatric symptoms (e.g. depression and apathy) have been reported to be associated with functional decline in HD (Sellers et al., 2020).

Social cognition includes functions that are used in all everyday situations with other people. These social cognitive functions, like interacting with other people or understanding the intentions of others, are often relevant for the functional capacities of people with HD, especially the more complex capacities like occupation, handling of finances and domestic responsibility which encompasses abilities of performing and understanding social negotiations. Despite the fact that social cognitive dysfunction can have negative effects on the daily lives of individuals with HD, the association between social cognitive dysfunction and the functional capacity in HD has to our knowledge only been investigated in a few studies, showing conflicting results

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(Brüne et al., 2011; Eddy et al., 2014; Ille et al., 2011; Tabrizi et al., 2013). The variability between the results from these studies stress the importance of more research on this subject. Moreover, reports regarding the social cognitive dysfunctions in HD are characterized by conflicting results, with some studies demonstrating social cognitive impairments in premanifest HD (Eddy et al., 2018; Eddy & Rickards, 2015b, 2015c; Stout et al., 2011), while other studies have not found reductions before the manifest stages of disease (Kipps et al., 2007; Larsen, Vinther-Jensen, Gade, et al., 2016; Milders et al., 2003). Also, there is an ongoing debate concerning the degree to which executive dysfunction affects the performance of HD gene expansion carrier on tasks of social cognition (Aboulafia-Brakha et al., 2011; Allain et al., 2011; Brüne et al., 2011; Eddy et al., 2014; Eddy & Rickards, 2015b). Tests developed for the examination of social cognition will also tap executive functions, attentional processes, and retrieval of information. When HD gene expansion carriers are impaired on tasks of social cognition, it is unknown whether it is the executive component in the task that is affected.

Methodological differences might explain the inconsistencies in the research-based facts on social cognitive dysfunction in HD. To date, *social cognition* as a domain remains poorly examined and most studies assessing social cognition in HD has primarily focused on tests of emotion recognition and theory of mind, using a standardized set of tests. In a meta-analysis by Bora et al. (2016), impairments of emotion recognition and theory of mind in premanifest and manifest HD gene expansion carriers were associated with disease burden, cognitive impairments, and proximity of onset of motor symptoms. However, there is an unmet need to study the consequences over time of having social cognitive dysfunction in HD.

In this study, we used a new methodological approach, where each participant was classified as impaired or not on two cognitive domains: *social cognition* and *executive functions*. The classifications were based on a comprehensive battery of tests applied in a large group of premanifest and motor-manifest HD gene expansion carriers. We investigated if the participants who were impaired on each of the cognitive domains were the same or if there was a significant difference between the participants who were impaired on *social cognition* and *executive functions*. Finally, we investigated which of these cognitive domains could predict a decline in the functional capacity of premanifest and motor-manifest HD gene expansion carriers over a 6-year follow-up period.

Methods

Participants

Time 1

The participants at Time 1 were ninety-eight HD gene expansion carriers enrolled in the study in year 2012–2013 from the Neurogenetics Clinic, Danish Dementia Research Centre, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark. The participants have been described previously (Vinther-Jensen et al., 2014) and were included based on the following criteria; a CAG repeat length $\geq$39, a Unified Huntington's Disease Rating Scale-99 total motor score (UHDRS-TMS) $\leq$55 (Huntington's Study Group, 1996), a Mini-Mental State Examination (MMSE) score $\geq$24 (Folstein et al., 1975), and a Montreal Cognitive Assessment (MoCA) score $\geq$19 (Nasreddine et al., 2005). The exclusion criteria were other neurological disease, ongoing alcohol- or drug abuse, or a native language other than Danish.

The participants were classified as premanifest HD gene expansion carriers, if they presented without substantial motor symptoms and had a UHDRS-TMS of $\leq$5. Contrarily, if their UHDRS-TMS was >5, they were classified as motor-manifest HD gene expansion carriers. This cutoff of >5 on the UHDRS-TMS scale to classify motor-manifest participants has previously been used in the TRACK-HD study (Tabrizi et al., 2009).

Time 2

The participants at Time 2 included HD gene expansion carriers who had previously participated at Time 1, and who agreed to take part in the follow-up examinations in year 2018–2020. All participants from Time 1 were contacted and invited to participate in the follow-up examinations. Included participants were again classified as premanifest and motor-manifest HD gene expansion carriers according to their UHDRS-TMS. They were assessed with the same tests and instruments as when participating at Time 1, but the focus of this follow-up study was their functional capacity score at Time 2. Time 2 participants were previously described in Hellem et al. (2021).

Controls

The control group consisted of forty-six previous at-risk individuals, who before inclusion in this study, were tested negative for the HD gene expansion (with a CAG repeat length of <30). They were included instead of unrelated healthy controls to better match for environmental and psychosocial factors. The control group was combined from control participants who were enrolled at Time 1 ($N = 39$), as well as new control participants enrolled at Time 2 ($N = 7$). Initial analyses showed that the controls at Time 1 and Time 2 did not differ significantly on demographic variables or on the functional capacity score (data not shown). Participants from Time 1 were assessed both at Time 1 and Time 2. However, all scores reported from the controls in this study were taken from their initial examination, meaning that only control participants who were enrolled at Time 2 had their scores from Time 2 included.

All participants and controls went through genetical counseling and were informed of their genetic status prior to and independently from enrollment in the study.

Procedure

This study was approved by the Ethics Committee of the Capital Region of Denmark (H2-2011-085 and H-17002606) and written informed consent was obtained from all participants before enrollment in the study. Inclusion involved participating in a neurological examination and a neuropsychological examination both at Time 1 and at Time 2. All examinations were completed by the same neurologists and neuropsychologists at Time 1 (TVJ and IUL, respectively) and at Time 2 (MNNH and RKH, respectively). During the neurological examination, participants were screened for depression and cognitive deficits using the Hamilton Depression Scale (HAM-17) (Hamilton, 1960), the MoCA (Nasreddine et al., 2005) and the MMSE (Folstein et al., 1975). Motor symptoms and functional capacity were examined with the UHDRS-TMS and the UHDRS-Total Functional Capacity (TFC) scale (Huntington's Study Group, 1996). The UHDRS-TFC is a 5-item interview assessing the functional capacities of persons with HD (Huntington's Study Group, 1996; Mestre et al., 2018). It covers basic functions of daily life (occupation, handling of finances, domestic responsibilities), as well as ADL functions (dressing, bathing, eating, level of care—home or facility). The UHDRS-TFC scale takes about 5 minutes to complete and a higher score (ranging from 0 to 13) indicates a better functional capacity. We used a ΔTFC score ($\text{UHDRS-TFC}_{\text{Time 1}} - \text{UHDRS-TFC}_{\text{Time 2}}$), to indicate the level of decline during the follow-up time.

Neuropsychological assessment

The neuropsychological assessment included tests of premorbid level of intelligence, psychomotor speed and attention, memory, visuospatial functions, executive functions, and social cognition. Here, only the tests of executive functions and social cognition are reported.

Executive functions were assessed using the Symbol Digit Modality test (SDMT) (Smith, 1982), the Trail Making test part B (TMT B) (Reitan, 1955), the Stroop test (100 items) (Stroop, 1935), the Verbal Lexical Fluency (FAS) (Lezak et al., 2004), the Verbal Lexical Alternating Fluency (K-B words) and the Verbal Semantic/Lexical Alternating Fluency (Food items-D words).

Social cognition was assessed with The Awareness of Social Inference Test (TASIT)—Social Inference-Minimal (SI-M) (McDonald et al., 2003), The Emotion Hexagon test (EH) (Calder et al., 1996; Sprengelmeyer et al., 1996), and the revised version of the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001). The TASIT SI-M is a task of sarcasm detection, where participants must detect sarcasm through the tone of voice and body language in videoclips portraying everyday situations between two people. The TASIT SI-M and the RMET were considered tasks of theory of mind and the EH were considered a task of emotion recognition. All tests have been described previously, and group results from the participants at Time 1 are presented in Larsen, Vinther-Jensen, Gade, et al. (2016) and Larsen, Vinther-Jensen, Nielsen, et al. (2016).

An educational index score (ranging from 8 to 17) was calculated for each participant based on the method previously used by Mortensen & Gade (1993). It represents the sum of years of schooling (ranging from 7 to 12 years) and the level of post-secondary education stratified into groups (ranging from 1 to 5).

Classification of cognitive impairments

In this study, we classified participants as impaired or not on two cognitive domains; *social cognition* and *executive functions,* based on their scores at Time 1. The methods for classifying impairments on the two cognitive domains were as follows.

Regression-based reference data were calculated correcting for age, sex, and educational index score for all executive and social cognitive tasks, based on the data from the control group. We calculated percentile estimates for the expected scores as the inverse of the normal cumulative distribution function specified by the regression model. For each task, each of the participant's observed score was compared to the estimated score from the relevant group. If the score was at or below the 10th percentile estimate for the relevant group, the participant was classified as impaired on that task. A classification of "Impaired on *social cognition*" was applied, if the participant was impaired on one or more of the social cognitive tasks. The classification of "Impaired on *executive functions*" was applied if the participant's scores on two or more tasks from the executive domain were impaired.

Statistical analysis

Group comparisons on the basic clinical information between participants and controls at Time 1 and Time 2, respectively, were performed using one-way analysis of variance or the Kruskal Wallis test, when the assumption of homogeneity of variances was not met. *Post hoc* comparisons were calculated using Dunnett's *t*-test or Pairwise Comparisons. Association analyses between demographic variables and test scores were performed using Pearson's r or Spearman's rho (for skewed distributions). A CAP score was calculated for all HD gene expansion carriers using the equation $\text{CAP} = \text{Age} \cdot (\text{CAG} - 35.5)$, by Penney et al., (1997). We used a Chi^2 analysis to examine if the participants who were impaired on the two cognitive domains (described above) were the same or if there was a significant difference between them. Finally, we used two multiple stepwise regression models for predicting the decline in UHDRS-TFC score across the follow-up time (using a ΔTFC score). The first model examined which of the two cognitive domains could explain the decline in UHDRS-TFC across the follow-up time, using the two categorical variables describing the impairments on the cognitive domains. We included age at Time 1, the UHDRS-TMS score at Time 1, and the HAM-17 depression score at Time 1 in the multiple regression model as confounding variables, to control for the effect of disease stage and neuropsychiatric symptoms in

the progression of the decline in TFC scores across the 6-year follow-up period. The second model examined which of the cognitive tasks could predict the decline in UHDRS-TFC score across the follow-up time, using the performance scores on the tasks of the predictive domain from the first model. Again, we included age at Time 1, the UHDRS-TMS score at Time 1, and the HAM-17 depression score at Time 1, as confounding variables.

The alpha level for significance was $p < .05$ for all analyses (two-tailed significance) and the Bonferroni-Holm correction was used to adjust the level of significance when multiple comparisons were performed.

Results

The follow-up time between Time 1 and Time 2 was on average 5.7 years (ranging from 4 to 7 years). Of the 98 participants from Time 1, 18 participants were not followed up at Time 2 (as illustrated in Figure 1). Of the participants lost to follow-up, 9 had died at Time 2 (1 premanifest and 8 motor-manifest HD gene expansion carriers), and 9 participants either declined to participate again or were unreachable despite our efforts (3 premanifest and 6 motor-manifest HD gene expansion carriers). In total, 80 participants (34 premanifest and 46 motor-manifest HD gene expansion carriers) were examined at Time 2. In the approximately 6 years between Time 1 and Time 2, 12 HD gene expansion carriers initially classified as premanifest were classified as motor-manifest at Time 2.

Table 1 presents the basic clinical information and the performance scores on all cognitive tests for the HD gene expansion carriers and controls at Time 1 and Time 2, by comparing the scores of the premanifest and motor-manifest HD gene expansion carriers with controls both at Time 1 and at Time 2, but scores between Time 1 and Time 2 were not statistically compared. At both Time 1 and Time 2, the motor-manifest HD gene expansion carriers had significantly higher age and UHDRS-TMS and significantly lower UHDRS-TFC and MoCA score than the premanifest HD gene expansion carriers at the respective time and the controls. At Time 1, the motor-manifest HD gene expansion carriers had a significantly higher HAM-17 score compared to the controls, while at Time 2, the HAM-17 score deviated significantly between the motor-manifest HD gene expansion carriers and the premanifest HD gene expansion carriers. The CAP score was significantly higher in the motor-manifest group compared to the premanifest HD gene expansion carriers and the controls both at Time 1 and Time 2. The distribution of CAP scores at Time 1 and Time 2 are shown in Figure 2. Also, the motor-manifest HD gene expansion carriers scored significantly different from the premanifest HD gene expansion carriers and the controls on almost all cognitive measures both at Time 1 and Time 2.

Table 2 presents a correlation matrix between the cognitive measures and the UHDRS-TFC at Time 1 and Time 2. Interestingly, the UHDRS-TFC was only significantly correlated with the EH at Time 2, and not with any social cognitive task at Time 1. Contrarily, the UHDRS-TFC was

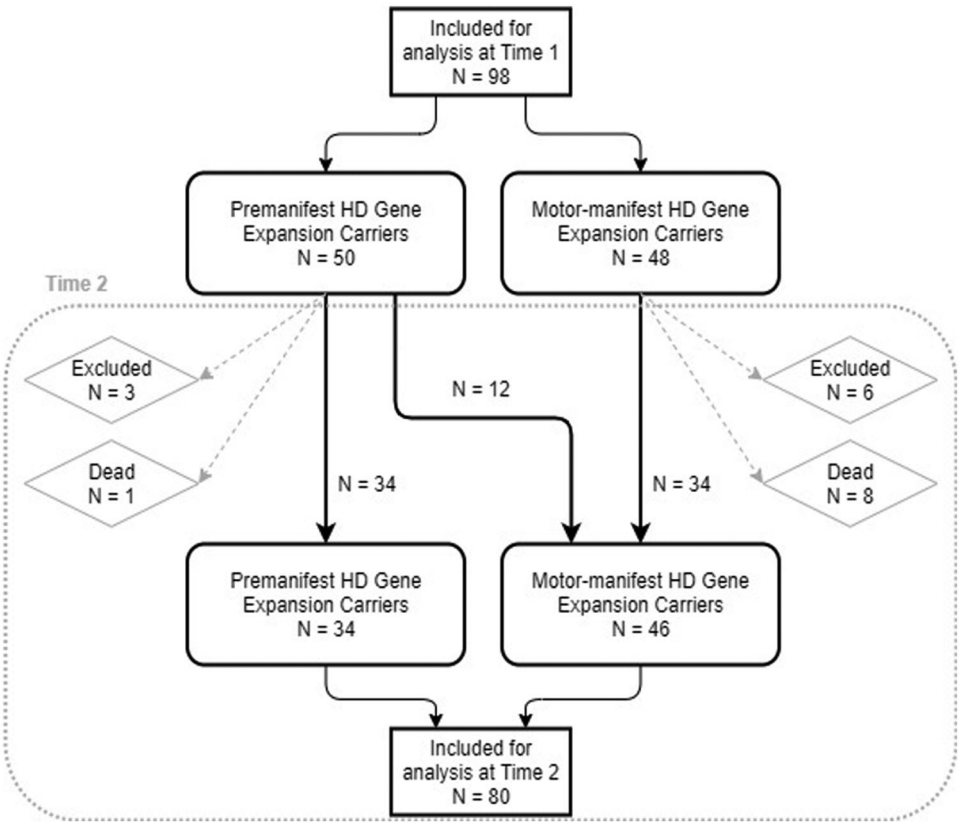

Figure 1. Diagram of participants included for analysis and classified as premanifest or motor-manifest HD gene expansion carriers at Time 1 and Time 2. HD = Huntington's Disease; N = Total number of participants.

Table 1. Basic clinical information and performance scores on the cognitive tests for the HD gene expansion carriers at Time 1 and Time 2, and the controls.

	HD Gene Expansion Carriers Time 1			HD Gene Expansion Carriers Time 2	
	Motor-Manifest	Premanifest	Controls	Motor-Manifest	Premanifest
N	48	50	46	46	34
Age (years)	51.2 (12.0)*†	36.5 (8.8)	42.0 (13.4)	52.89 (11.6)*‡	41.15 (8.5)
Sex (M/F)	29/19	29/21	20/26	25/21	21/13
CAP score	369.2 (101.9)†	240.1 (90.9)	–	389.8 (110.4)‡	247.6 (82.9)
UHDRS-TMS	19.7 (8.0)*†	1.9 (1.5)*	0.4 (0.9)	30.3 (18.7)*‡	1.8 (1.7)*
UHDRS-TFC Score	10.0 (1.9)*†	12.9 (0.5)	13.0 (0.2)	8.4 (2.8)*‡	12.9 (0.5)
MoCA Score[a]	25.6 (2.1)*†	28.1 (1.4)	28.0 (1.5)	23.8 (3.9)*‡	28.2 (2.2)
HAM-17 Score[b]	5.9 (3.9)*	4.5 (4.7)	2.9 (3.8)	4.3 (3.7)‡	2.1 (2.0)
Social Cognition					
EH Score[c]	15.1 (3.0)*†	18.8 (2.5)	18.9 (2.7)	16.0 (4.8)‡	19.7 (2.3)
RMET Score[c]	19.5 (4.3)*†	25.1 (3.9)	24.5 (3.5)	20.3 (5.6)*‡	26.0 (2.9)
TASIT SI-M, %[c]	76.8 (11.4)*†	90.8 (5.0)	89.1 (6.5)	79.5 (9.6)*‡	88.6 (5.9)
Executive Functions					
Alternating Lexical Fluency Score (K-B)[d]	10.1 (3.9)*†	14.8 (3.2)*	16.5 (3.3)	10.7 (4.8)*‡	15.6 (3.2)
Alternating Semantic/Lexical Fluency Score (Food-D)[d]	7.9 (2.8)*†	11.5 (3.3)*	13.6 (3.5)	8.3 (4.3)*‡	13.2 (3.4)
SDMT Score[e]	29.9 (8.5)*†	49.7 (8.2)	56.2 (10.8)	53.2 (11.1)*‡	33.4 (14.4)
Stroop Incongruence, Sec[f]	174.5 (54.5)*†	118.9 (21.2)	107.9 (22.6)	181.7 (96.3)*‡	108.0 (24.3)
TMT B, Sec[g]	124.0 (53.2)*†	62.0 (16.8)	55.8 (19.7)	103.9 (64.5)*‡	43.6 (15.4)*
Verbal Lexical Fluency Score (FAS)[h]	27.3 (10.6)*†	37.2 (10.2)	41.5 (11.0)	29.6 (14.6)*‡	45.3 (10.4)

Data is presented as mean (SD) unless otherwise noted.

Note. * Statistically significant difference from the controls ($p < .05$). †Statistically significant difference from the premanifest HD at Time 1 ($p < .05$). ‡Statistically significant difference from the premanifest HD at Time 2 ($p < .05$).

EH = Emotion Hexagon; HAM-17 = Hamilton Depression Scale; HD = Huntington's Disease; MoCA = Montreal Cognitive Assessment; N = Total number of participants; RMET = Reading the Mind in the Eyes Test; SDMT = Symbol Digit Modality Test; SI-M = Social Inference Minimal; TASIT = The Awareness of Social Inference Test; TFC = Total Functional Capacity; TMS = Total Motor Score; TMT = Trail Making Test; UHDRS = Unified Huntington's Disease Rating Scale.

[a]Data missing from 5 premanifest and 5 motor-manifest HD gene expansion carriers at Time 2. [b]Data missing from 6 premanifest and 6 motor-manifest HD gene expansion carriers at Time 2. [c]Data missing from one control and 6 premanifest and 9 motor-manifest HD gene expansion carriers at Time 2. [d]Data missing from 7 premanifest and 17 motor-manifest HD gene expansion carriers at Time 2. [e]Data missing from 2 premanifest and 18 motor-manifest HD gene expansion carriers at Time 2. [f]Data missing from one premanifest HD gene expansion carrier at Time 1 and 6 premanifest and 15 motor-manifest HD gene expansion carriers at Time 2. [g]Data missing from 6 premanifest and 14 motor-manifest HD gene expansion carriers at Time 2. [h]Data missing from 7 premanifest and 14 motor-manifest HD gene expansion carriers at Time 2.

significantly associated with several executive tasks both at Time 1 and Time 2. Several significant correlations were found between social cognitive tests and executive tests at Time 1 and at Time 2.

Approximately one third of the HD gene expansion carriers were impaired on each of the social cognitive tests according to the defined criteria (see Table 3). When combining their performance on the domain of *social cognition*, 51% of the HD gene expansion carriers were impaired on one or more of the social cognitive tests. More than half of the participants had reduced scores on two or more of the executive tests, classifying them as impaired on *executive functions*.

Although the frequencies of participants who were impaired on *social cognition* and *executive functions* were almost equal, the participants who were impaired on each of the domains were not necessarily the same participants. Thus, we examined if there was a significant difference between the HD gene expansion carriers who were impaired on *social cognition* compared to *executive functions* (see Figure 3). The HD gene expansion carriers who were classified as impaired on *social cognition* were significantly different from the HD gene expansion carriers classified as impaired on *executive functions* ($Chi^2 = 29.854$, $p < .001$).

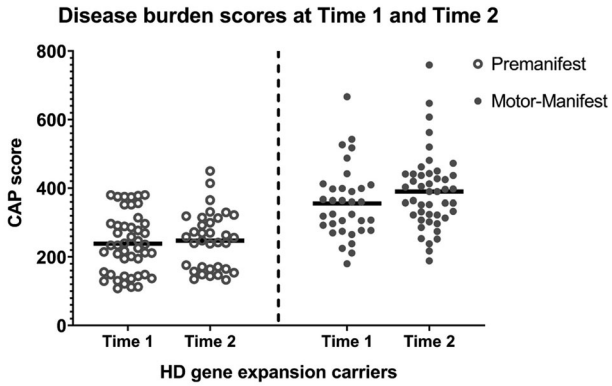

Figure 2. Scatter Dot Plot showing the distribution of CAP scores in premanifest and motor-manifest HD gene expansion carriers at Time 1 and Time 2. The bars represent the mean value of the group.

Decline in the UHDRS-TFC score

We used a ΔTFC score to indicate the difference in UHDRS-TFC score across the six years follow-up interval, with a higher score representing a larger decline in UHDRS-TFC score at Time 2, compared to Time 1. The UHDRS-TFC score had on average decreased by 2.3 points for the motor-manifest group at Time 2 ($\bar{x} = 2.3$, SD = 2.2). For the pre-manifest group at Time 2, the UHDRS-TFC score had decreased by 0.1 point ($\bar{x} = 0.1$, SD = 0.5).

We examined whether one or both cognitive domains could predict the decline in UHDRS-TFC across the follow-up period, using the ΔTFC score. In a multiple stepwise regression model, with the two categorical cognitive variables (describing the impairments on the cognitive domains) as independent variables together with age at Time 1, UHDRS-TMS at Time 1, and the HAM-17 score at Time 1, the UHDRS-TMS and impairments on *social cognition* were significant predictors of the decline in UHDRS-TFC score (see Table 4). When the participants were impaired on social cognitive functions, the difference between their UHDRS-TFC score at Time 1 and Time 2 were 1.073 higher, than when the participants were not impaired on *social cognition*. This model explained 32% of the total variance.

In a second regression model, we examined which social cognitive functions could predict the decline in the UHDRS-TFC, using the ΔTFC. We entered the performance scores from the three social cognitive tasks at Time 1 as independent variables into a new multiple stepwise regression model, with age at Time 1, UHDRS-TMS at Time 1, and the HAM-

Table 3. The percentage of participants classified as impaired on each of the social cognitive tasks and frequency of impairment on the domains; social cognition and executive functions for all HD Gene Expansion Carriers (N = 98) at Time 1.

	RMET	EH	TASIT SI-M	*Social cognition*	*Executive functions*
Impairment					
Yes	29%	38%	28%	51%*	55%
No	71%	62%	72%	49%	45%
Total	100%	100%	100%	100%	100%

Note. * Statistically significantly different from *Executive Functions* ($p < .05$).
EH = Emotion Hexagon test; HD = Huntington's Disease; N = Total number of participants; RMET = Reading the Mind in the Eyes test; SI-M = Social Inference-Minimal; TASIT = The Awareness of Social Inference test.

Table 2. Correlation matrix on the Social Cognitive and Executive tasks and the UHDRS-TFC for the motor-manifest HD Gene Expansion Carriers.

	1.	2.[a]	3.[a]	4.[a]	5.	6.	7.[b]	8.	9.[c]	10.[c]
1. UHDRS-TFC	…	.25	.46*	.18	.61**	−.53*	−.39*	.56*	.46*	.53*
2. RMET score	.06	…	.79**	.63**	.58*	−.57*	−.69**	.47*	.71**	.46*
3. EH score	.06	.47*	…	.54*	.60*	−.58*	−.52*	.47*	.58*	.45*
4. TASIT SI-M score	.01	.49**	.43*	…	.52*	−.59*	−.49*	.56*	.46*	.28
5. SDMT score	.37*	.38*	.56**	.46*	…	−.87**	−.80**	.83**	.74**	.65**
6. TMT B score	−.33*	−.57**	−.56**	−.41*	−.77**	…	.76**	−.75**	−.66**	−.54*
7. Stroop Interference score	−.17	−.40*	−.38*	−.54**	−.72**	.64**	…	−.83**	−.88**	−.55*
8. Lexical Fluency (FAS) score	.19	.47*	.40*	.31*	.47*	−.53**	−.59**	…	.85**	.59*
9. Alternating Fluency (K-B) score	.25	.38*	.24	.07	.42*	−.47*	−.55**	.69**	…	.69**
10. Alternating Fluency (Food-D) score	.20	.22	.30*	.25	.37*	−.31*	−.55**	.56**	.56**	…

Note. Correlations below the dotted line is from Time 1 ($N = 48$) and correlations above the dotted line is from Time 2 ($N = 32$). * Statistically significant at the level of $p < .05$. **Statistically significant at the level of $p < .001$.
EH = Emotional Hexagon; RMET = Reading the Minds in the Eyes test; SDMT = Symbol Digit Modality Test; SI-M = Social Inference Minimal; TASIT = The Awareness of Social Inference test; TMT: Trail Making Test; UHDRS-TFC = Unified Huntington Disease Rating Scale – Total Functional Capacity.
[a]Data missing from 5 motor-manifest HD gene expansion carriers at Time 2. [b]Data missing from one motor-manifest HD gene expansion carrier at Time 2. [c]Data missing from three motor-manifest HD gene expansion carriers at Time 2.

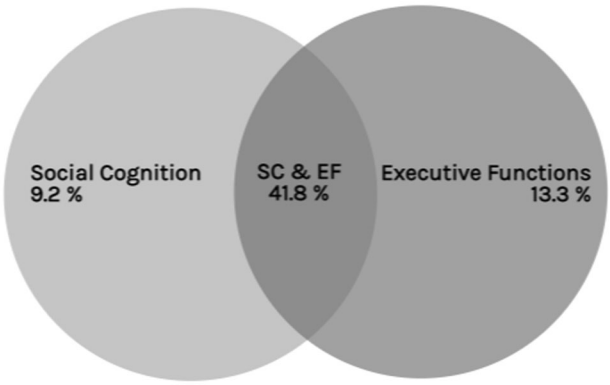

Figure 3. Venn Diagram describing the distribution of the HD gene expansion carriers who were impaired on the two cognitive domains (frequency in percentage presented). Note that 35.7% of the HD gene expansion carriers were not impaired on any cognitive domain (not presented in the figure). SC = Social cognition; EF = Executive functions.

Table 4. Model parameter estimates from the two multiple stepwise regression models with the ΔTFC as outcome variable for all HD gene expansion carriers.

	Variables in the model	b	Std. Error	R^2 Change	*p*-level
Model 1*	Constant	0.219	0.269		.417
	UHDRS-TMS	0.075	0.025	.275	.004
	Impairment of *social cognition*	1.075	0.483	.044	.029
Model 2**	Constant	3.864	1.428		.008
	UHDRS-TMS	0.073	0.025	.275	.004
	Emotion Hexagon	−0.181	0.074	.053	.016

Note. * R^2 = .319. ** R^2 = .328.
TFC = Total Functional Capacity; HD = Huntington's Disease; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

17 score at Time 1 as confounding variables and the ΔTFC as the dependent variable. In this model, the UHDRS-TMS and the EH test significantly predicted the decline in UHDRS-TFC score and could explain 33% of the total variance. A lower performance on the EH test at Time 1, was associated with a larger decline in the UHDRS-TFC score across the follow-up period, corresponding to a difference of 0.18 points on the TFC scale for each lost point on the EH test.

Discussion

In this follow-up study we investigated whether the initial performance on one or both of two cognitive domains; *social cognition* and *executive functions* could predict the decline in UHDRS-TFC in a large sample of premanifest and motor-manifest HD gene expansion carriers during a 6-year follow-up period. A new methodological approach was used, where we applied a comprehensive battery of neuropsychological tests and categorized impairments based on regression-based normative data from healthy controls. With this method, each domain incorporated several tests on different functions and relevant background variables were corrected for when classifying impairments. The domain of *social cognition* included tests on emotion recognition and theory of mind (including a test of sarcasm detection). Thus, while using the power of an entire domain instead of single tests to predict the decline in UHDRS-TFC score, the social cognitive domain in this study also incorporated sarcasm detection as a theory of mind task, which is not traditionally assessed in HD studies (Bora et al., 2016; Snowden, 2017).

We aimed to address the debate concerning an association between social cognition and executive functions, by investigating if the participants who were impaired on the domains *social cognition* and *executive functions* were different. The results showed that the participants classified as impaired on *social cognition* were significantly different from the participants impaired on *executive functions,* meaning that the participants who were classified as impaired on *social cognition* were not the same participants as the ones who were categorized as impaired on *executive functions*. It can be discussed whether this difference illustrate a genuine endophenotypic difference between patients, where some patients are more affected by social cognitive dysfunction than others, or whether it is a question of differences in disease course. However, the result is in accordance with results from previous studies (Eddy & Rickards, 2015b, 2015c), where impairments on tasks of theory of mind were found independently of executive dysfunction in HD. Yet, in other studies, significant correlations between tasks of theory of mind and executive functions have been demonstrated (Allain et al., 2011; Brüne et al., 2011; Eddy et al., 2014). The previous studies have primarily measured social cognitive functions and executive functions with single tests and have not taken the multifaceted nature of the constructs into account (as pointed out by Aboulafia-Brakha et al. (2011)). In this study, we incorporated several tests into each domain to account for the multifaceted constructs and to examine the *abilities* of individuals with HD, instead of examining associations between isolated test performances. Although several social cognitive and executive tasks were significantly associated, the present results also showed a significant difference between the domains *executive functions* and *social cognition* indicating that social cognition includes unique and separate functions in HD, which cannot solely be accounted for by the executive dysfunction found in this patient group.

Importantly, this result was not simply a consequence of the participants being very impaired on *executive functions* at Time 1. As presented in Table 2, the frequency of impairments was equally large on *executive functions* and *social cognition* at Time 1.

The decline in UHDRS-TFC score across the 6 years follow-up interval in the present study was significantly predicted by impairments of *social cognition* and the UHDRS-TMS at Time 1. This result was of clinical interest, as it could help inform the clinician on the patient's course of disease, when social cognitive impairments are present. When constructing the model, we entered age, HAM-17 and UHDRS-TMS at Time 1, along with the two categorical cognitive domains. Even when taking these measures into account, only the UHDRS-TMS and the impairments of *social cognition* could explain the decrease in the UHDRS-TFC score. Neither age nor depression at Time 1 predicted the decline in UHDRS-TFC score significantly, when

impairments of *social cognition* and UHDRS-TMS were entered into the model. Also, while executive dysfunction naturally will affect the functional capacity and abilities of daily living in HD gene expansion carriers, this cognitive domain could not be used to predict the progression of functional symptoms over time, as it was not included in the regression model. In contrast, the unique and separate functions in the domain of *social cognition* did contribute significantly to the prediction of the progression of functional symptoms.

It has previously been shown that functional decline is associated with motor symptoms (Beglinger et al., 2010; Tabrizi et al., 2013), but only few studies have investigated the association between functional capacity and social cognitive functions in HD (Brüne et al., 2011; Eddy et al., 2014; Ille et al., 2011; Tabrizi et al., 2013). Ille et al. (2011) found a significant association between functional capacity and recognition of happiness and surprise. In the TRACK-HD study, functional capacity was significantly associated with anger, disgust and surprise, but no significant association was found with the total emotion recognition score (Tabrizi et al., 2013). Eddy et al. (2014) found a significant correlation between total functional capacity and the RMET, as well as the *faux pas* task. In contrast, Brüne et al. (2011) did not report a significant correlation between theory of mind and UHDRS-TFC. The present study shows the predictive power of *social cognition* as an entire domain for functional decline. A considerable strength of the results was the outcome variable, with a 6 years long follow-up interval, substantially longer than compared to previous longitudinal studies in motor-manifest HD gene expansion carriers (Schobel et al., 2017; Tabrizi et al., 2013). The association may be caused by the involvement of social cognitive functions in several activities of daily living (e.g. reliance on social relations, communication, and self-regulation). On average, the UHDRS-TFC score was decreased by 2.3 points in motor-manifest HD gene expansion carriers over 6 years of follow-up (despite wide variability). In contrast, the premanifest HD gene expansion carriers, who remained in the premanifest stage of disease, did not decrease considerably in functional capacity. These results deviates from the large-scale TRACK-HD cohort study, where premanifest and motor-manifest participants were followed-up for up to 36 months (Tabrizi et al., 2013). Their results revealed that diagnosed (motor-manifest) participants decreased annually in UHDRS-TFC score by 0.14 points (after adjusting for CAG repeat length and age), corresponding to 0.84 after 6 years. This is considerably lower than our result, but while we included 46 participants in the motor-manifest group, only 19 participants were included in the diagnosed group of TRACK-HD at 36 months of follow-up (Tabrizi et al., 2013).

When the single tests in the domain of *social cognition* were investigated, we found the EH task to be the only significant predictor of the decline in UHDRS-TFC score, together with the UHDRS-TMS. This was a somewhat surprising finding, considering that the motor-manifest HD gene expansion carriers scored significantly lower than the premanifest HD gene expansion carriers and the controls on the other social cognitive tests as well (see Table 1). Thus, theory of mind could not contribute to the prediction of the decline in UHDRS-TFC. Previous studies have found variability in associations between social cognitive impairments and functional capacities, particularly when examining theory of mind (Brüne et al., 2011; Eddy et al., 2014; Ille et al., 2011; Tabrizi et al., 2013). Proposedly, these inconsistencies might be a result of the tests used in the study. While RMET is often used as a theory of mind task, it has been argued that RMET draws on emotion recognition abilities to a larger degree (Oakley et al., 2016). Thus, while theory of mind might be associated with functional capacities, abilities used in the RMET task might not be. Moreover, it seems that emotion recognition affects functional capacities to a higher degree than other social functions, even functions involved in perceiving tone of voice and body language as in the sarcasm detection task. Similar results were found by Ille et al. (2011) and Tabrizi et al. (2013). Impairments on tasks of emotion recognition, specifically negative emotions, have continuously been demonstrated in HD gene expansion carriers (Bora et al., 2016; Henley et al., 2008, 2012; Paulsen, 2011; Snowden, 2017), but discussions concerning when these impairments arise and whether performance on tasks examining these functions are affected by executive dysfunction persists.

In the present study, it was not investigated whether the *changes* in *social cognition* and *executive functions* could lead to changes in UHDRS-TFC. Instead, this study focused on the clinical relevance of the initial cognitive performance on the course of disease. Investigating the longitudinal changes in cognitive functions could have contributed with relevant information on the disease progression and associations between the impairments in different cognitive domains across time. However, this was not an aim of the present study.

The functional abilities of the HD gene expansion carriers were only examined with one measure (the UHDRS-TFC scale). While we believe that the UHDRS-TFC is a sound measure, it would be interesting to examine, if the same results could be found with other measures of functional abilities. Another widely used assessment of functional abilities in HD is the UHDRS-Functional Assessment Scale (Huntington's Study Group, 1996; Mestre et al., 2018), which is considered an extension to the UHDRS-TFC scale. The UHDRS-Functional Assessment Scale would have been a relevant additional measure in the present study (but was not applied at Time 1).

There are other limitations in this study that needs mentioning. First, the criteria for being categorized as impaired varied across the two domains. Where impairment on *social cognition* only required one impaired test performance, impairment on *executive functions* was based on two impaired test performances. These criteria were essentially methodological decisions that were based on clinical experience and theoretical discussions. However, these methodological decisions created potential confounding bias in our results, which means that the results should be interpreted with caution. Second, as this study was a follow up study there is a potential bias from practice effects, when

participants are examined with the same neuropsychological tests within a period. The tests used in the present study also had some overlap with the tests used in the ENROLL-HD battery, which makes the discussion of practice effects highly relevant. However, as our main result was based on the results from Time 1 only, we do not believe this bias to have affected our results to a larger degree than in other studies, where tests from the ENROLL-HD battery are included. Third, our control group consisted of gene-negative family members. We included these individuals to control for psychosocial and environmental factors, which we believe were very important in the present study. However, the use of this control group instead of unrelated individuals do mean that comparisons with the general population and other control groups are more difficult. Finally, it should be mentioned that the follow-up time for the participants varied between 4 and 7 years. This interval includes a rather big difference, specifically when the participants have a neurodegenerative disease as in the present study and this could have affected the results.

Conclusively, this study found that the decline in UHDRS-TFC scores over 6 years of follow-up in a large group of pre-manifest and motor-manifest participants were predicted by impairments of *social cognition* and the UHDRS-TMS at their initial examination. The EH test and the UHDRS-TMS at Time 1 were the only significant predictors of the decline in UHDRS-TFC, when all social cognitive tests were entered a multiple stepwise regression model. Moreover, impairments of *executive function* could not explain the decline in UHDRS-TFC when impairments of *social cognition* were assessed, although several executive tasks were significantly correlated with the UHDRS-TFC. Thus, social cognitive impairments—specifically emotion recognition—can have a significant impact on the functional decline in HD. This result emphasizes the importance of regular assessment of social cognitive dysfunction in HD and the predictive value of social cognitive impairments for the progression of disease.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Aboulafia-Brakha, T., Christe, B., Martory, M. D., & Annoni, J. M. (2011). Theory of mind tasks and executive functions: A systematic review of group studies in neurology. *Journal of Neuropsychology*, *5*(Pt 1), 39–55. https://doi.org/10.1348/174866410X533660

Allain, P., Havet-Thomassin, V., Verny, C., Gohier, B., Lancelot, C., Besnard, J., Fasotti, L., & Le Gall, D. (2011). Evidence for deficits on different components of theory of mind in Huntington's disease. *Neuropsychology*, *25*(6), 741–751. https://doi.org/10.1037/a0024408

Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The "Reading the Mind in the Eyes" Test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry*, *42*(2), 241–251. https://doi.org/10.1017/S0021963001006643

Beglinger, L. J., O'Rourke, J. J. F., Wang, C., Langbehn, D. R., Duff, K., & Paulsen, J. S. (2010). Earliest functional declines in Huntington disease. *Psychiatry Research*, *178*(2), 414–418. https://doi.org/10.1016/j.psychres.2010.04.030

Bora, E., Velakoulis, D., & Walterfang, M. (2016). Social cognition in Huntington's disease: A meta-analysis. *Behavioural Brain Research*, *297*, 131–140. https://doi.org/10.1016/j.bbr.2015.10.001

Brüne, M., Blank, K., Witthaus, H., & Saft, C. (2011). "Theory of mind" is impaired in Huntington's disease". *Movement Disorders*, *26*(4), 671–678. https://doi.org/10.1002/mds.23494

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial emotion recognition after Bilateral Amygdala Damage: Differentially severe impairment of fear. *Cognitive Neuropsychology*, *13*(5), 699–745. https://doi.org/10.1080/026432996381890

Eddy, C. M., & Rickards, H. E. (2015a). Cognitive deficits predict poorer functional capacity in Huntington's disease: But what is being measured? *Neuropsychology*, *29*(2), 268–273. https://doi.org/10.1037/neu0000134

Eddy, C. M., & Rickards, H. E. (2015b). Interaction without intent: The shape of the social world in Huntington's disease. *Social Cognitive and Affective Neuroscience*, *10*(9), 1228–1235. https://doi.org/10.1093/scan/nsv012

Eddy, C. M., & Rickards, H. E. (2015c). Theory of mind can be impaired prior to motor onset in Huntington's disease. *Neuropsychology*, *29*(5), 792–798. https://doi.org/10.1037/neu0000190

Eddy, C. M., Rickards, H. E., & Hansen, P. C. (2018). Through your eyes or mine? The neural correlates of mental state recognition in Huntington's disease. *Human Brain Mapping*, *39*(3), 1354–1366. https://doi.org/10.1002/hbm.23923

Eddy, C. M., Sira Mahalingappa, S., & Rickards, H. E. (2014). Putting things into perspective: The nature and impact of theory of mind impairment in Huntington's disease. *European Archives of Psychiatry and Clinical Neuroscience*, *264*(8), 697–705. https://doi.org/10.1007/s00406-014-0498-4

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). 'Mini-Mental State' a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.3744/snak.2003.40.2.021

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*, 56–62. https://doi.org/10.1192/bjp.bp.107.040485

Hellem, M. N. N., Hendel, R. K., Vinther-Jensen, T., Larsen, I. U., Nielsen, T. T., Hjermind, L. E., Budtz-Jørgensen, E., Vogel, A., & Nielsen, J. E. (2021). Endophenotypical drift in Huntington's disease: A 5-year follow-up study. *Orphanet Journal of Rare Diseases*, *16*(1), 1–11. https://doi.org/10.1186/s13023-021-01967-2

Henley, S. M. D., Novak, M. J. U., Frost, C., King, J., Tabrizi, S. J., & Warren, J. D. (2012). Emotion recognition in Huntington's disease: A systematic review. *Neuroscience and Biobehavioral Reviews*, *36*(1), 237–253. https://doi.org/10.1016/j.neubiorev.2011.06.002

Henley, S. M. D., Wild, E. J., Hobbs, N. Z., Warren, J. D., Frost, C., Scahill, R. I., Ridgway, G. R., MacManus, D. G., Barker, R. A., Fox, N. C., & Tabrizi, S. J. (2008). Defective emotion recognition in early

HD is neuropsychologically and anatomically generic. *Neuropsychologia*, *46*(8), 2152–2160. https://doi.org/10.1016/j.neuropsychologia.2008.02.025

Huntington's Study Group. (1996). Unified Huntington's Disease Rating Scale: Reliability and consistency. *Movement Disorders*, *11*(2), 136–142.

Ille, R., Holl, A. K., Kapfhammer, H. P., Reisinger, K., Schäfer, A., & Schienle, A. (2011). Emotion recognition and experience in Huntington's disease: Is there a differential impairment? *Psychiatry Research*, *188*(3), 377–382. https://doi.org/10.1016/j.psychres.2011.04.007

Kipps, C. M., Duggins, A. J., McCusker, E. A., & Calder, A. J. (2007). Disgust and happiness recognition correlate with anteroventral insula and amygdala volume respectively in preclinical Huntington's disease. *Journal of Cognitive Neuroscience*, *19*(7), 1206–1217. https://doi.org/10.1162/jocn.2007.19.7.1206

Larsen, I. U., Vinther-Jensen, T., Gade, A., Nielsen, J. E., & Vogel, A. (2016). Do I Misconstrue? Sarcasm detection, emotion recognition, and theory of mind in Huntington disease. *Neuropsychology*, *30*(2), 181–189. https://doi.org/10.1037/neu0000224

Larsen, I. U., Vinther-Jensen, T., Nielsen, J. E., Gade, A., & Vogel, A. (2016). Social cognition, executive functions and self-report of psychological distress in Huntington's disease. *PLoS Currents*, *8*(Huntington Disease), 1–20. https://doi.org/10.1016/j.jalz.2017.06.501

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). Verbal functions and language skills. In M. D. Lezak, D. B. Howieson, & D. W. Loring (Eds.), *Neuropsychological assessment* (4th ed., pp. 501–530). Oxford University Press.

McColgan, P., & Tabrizi, S. J. (2018). Huntington's Disease: A clinical review. *European Journal of Neurology*, *25*(1), 24–34. https://doi.org/10.1111/ene.13413

McDonald, S., Flanagan, S., Rollins, J., & Kinch, J. (2003). A new clinical tool for assessing social perception after traumatic brain injury. *The Journal of Head Trauma Rehabilitation*, *18*(3), 219–238.

Mestre, T. A., Busse, M., Davis, A. M., Quinn, L., Rodrigues, F. B., Burgunder, J. M., Carlozzi, N. E., Walker, F., Ho, A. K., Sampaio, C., Goetz, C. G., Cubo, E., Martinez-Martin, P., & Stebbins, G. T. (2018). Rating scales and performance-based measures for assessment of functional ability in Huntington's Disease: Critique and recommendations. *Movement Disorders Clinical Practice*, *5*(4), 361–372. https://doi.org/10.1002/mdc3.12617

Milders, M., Crawford, J. R., Lamb, A., & Simpson, S. A. (2003). Differential deficits in expression recognition in gene-carriers and patients with Huntington's disease. *Neuropsychologia*, *41*(11), 1484–1492. https://doi.org/10.1016/S0028-3932(03)00079-4

Mortensen, E. L., & Gade, A. (1993). On the relation between demographic variables and neuropsychological test performance. *Scandinavian Journal of Psychology*, *34*(4), 305–317. https://doi.org/10.1111/j.1467-9450.1993.tb01127.x

Nasreddine, Z. S., Phillips, N. A., BÃ©dirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221

Oakley, B. F. M., Brewer, R., Bird, G., & Catmur, C. (2016). Theory of mind is not theory of emotion: A cautionary note on the reading the mind in the eyes test. *Journal of Abnormal Psychology*, *125*(6), 818–823. https://doi.org/10.1037/abn0000182

Paulsen, J. S. (2011). Cognitive impairment in Huntington Disease: Diagnosis and treatment. *Current Neurology and Neuroscience Reports*, *11*(5), 474–483. https://doi.org/10.1038/jid.2014.371

Paulsen, J. S., Langbehn, D. R., Stout, J. C., Aylward, E., Ross, C. A., Nance, M., Guttman, M., Johnson, S., MacDonald, M., Beglinger, L. J., Duff, K., Kayson, E., Biglan, K., Shoulson, I., Oakes, D., & Hayden, M. (2008). Detection of Huntington's disease decades before diagnosis: The predict-HD study. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(8), 874–880. https://doi.org/10.1136/jnnp.2007.128728

Penney, J. B., Vonsattel, J.-P., MacDonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's Disease. *Annals of Neurology*, *41*(5), 689–692.

Reitan, R. M. (1955). The relation of the Trail Making Test to organic brain damage. *Journal of Consulting Psychology*, *19*(5), 393–394. https://doi.org/10.1037/h0044509

Schobel, S. A., Palermo, G., Auinger, P., Long, J. D., Ma, S., Khwaja, O. S., Trundell, D., Cudkowicz, M., Hersch, S., Sampaio, C., Dorsey, E. R., Leavitt, B. R., Kieburtz, K. D., Sevigny, J. J., Langbehn, D. R., & Tabrizi, S. J. (2017). Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. *Neurology*, *89*(24), 2495–2502. https://doi.org/10.1212/WNL.0000000000004743

Sellers, J., Ridner, S. H., & Claassen, D. O. (2020). A systematic review of neuropsychiatric symptoms and functional capacity in Huntington's Disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *32*(2), 109–124. https://doi.org/10.1176/appi.neuropsych.18120319

Smith, A. (1982). *Symbol digit modalities test: Manual*. Western Psychological Services.

Snowden, J. S. (2017). The neuropsychology of Huntington's Disease. *Archives of Clinical Neuropsychology*, *32*(7), 876–887. https://doi.org/10.1093/arclin/acx086

Sprengelmeyer, R., Young, A. W., Calder, A. J., Karnat, A., Lange, H., Hömberg, V., Perrett, D. I., & Rowland, D. (1996). Loss of disgust: Perception of faces and emotions in Huntington's disease. *Brain*, *119*(5), 1647–1665. https://doi.org/10.1093/brain/119.5.1647

Stout, J. C., Paulsen, J. S., Queller, S., Solomon, A. C., Whitlock, K. B., Campbell, J. C., Carlozzi, N., Duff, K., Beglinger, L. J., Langbehn, D. R., Johnson, S. A., Biglan, K. M., & Aylward, E. H. (2011). Neurocognitive signs in prodromal Huntington Disease. *Neuropsychology*, *25*(1), 1–14. https://doi.org/10.1037/a0020937

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A., Durr, A., Craufurd, D., Kennard, C., Hicks, S. L., Fox, N. C., Scahill, R. I., Borowsky, B., Tobin, A. J., Rosas, H. D., Johnson, H., Reilmann, R., Landwehrmeyer, B., & Stout, J. C. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet. Neurology*, *8*(9), 791–801. https://doi.org/10.1016/S1474-4422(09)70170-X

Tabrizi, S. J., Scahill, R. I., Owen, G., Durr, A., Leavitt, B. R., Roos, R. A., Borowsky, B., Landwehrmeyer, B., Frost, C., Johnson, H., Craufurd, D., Reilmann, R., Stout, J. C., & Langbehn, D. R. (2013). Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: Analysis of 36-month observational data. *The Lancet Neurology*, *12*(7), 637–649. https://doi.org/10.1016/S1474-4422(13)70088-7

Vinther-Jensen, T., Larsen, I. U., Hjermind, L. E., Budtz-Jørgensen, E., Nielsen, T. T., Nørremølle, A., Nielsen, J. E., & Vogel, A. (2014). A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. *Orphanet Journal of Rare Diseases*, *9*(114), 114–119.

Walker, F. O. (2007). Huntington's disease. *Lancet*, *369*(9557), 218–228. https://doi.org/10.1016/S0140-6736(07)60111-1

MANUSCRIPT IV

An Exploratory Study Investigating Autonomy in Huntington Disease Gene Expansion Carriers

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Research Report

An Exploratory Study Investigating Autonomy in Huntington's Disease Gene Expansion Carriers

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Abstract.
Background: Autonomy describes a psychological state of self-regulation of motivation and action, which is a central characteristic of healthy functioning. In neurodegenerative diseases measures of self-perception have been found to be affected by the disease. However, it has never been investigated whether measures of self-perception, like autonomy, is affected in Huntington's disease.
Objective: We investigated whether autonomy is affected in Huntington's disease and if the degree of autonomy is associated with motor function, neuropsychiatric symptoms, cognitive impairments, and apathy.
Methods: We included 44 premanifest and motor-manifest Huntington's disease gene expansion carriers and 19 controls. Autonomy was examined using two self-report questionnaires, the Autonomy-Connectedness Scale-30 and the Index of Autonomous Functioning. All participants were examined according to motor function, cognitive impairments, and neuropsychiatric symptoms, including apathy.
Results: Statistically significant differences were found between motor-manifest Huntington's disease gene expansion carriers and premanifest Huntington's disease gene expansion carriers or controls on two measures of autonomy. Between 25–38% of motor-manifest Huntington's disease gene expansion carriers scored significantly below the normal level on subscales of autonomy as compared to controls. One autonomy subscale was associated with apathy ($r = -0.65$), but not with other symptoms of Huntington's disease.
Conclusion: This study provides evidence for impaired autonomy in individuals with Huntington's disease and an association between autonomy and apathy. The results underline the importance of maintaining patient autonomy and involvement in care throughout the disease.

Keywords: Apathy, autonomy, Huntington's disease, neuropsychiatric symptoms, self-perception

INTRODUCTION

Autonomy is a theoretical construct that describes a psychological state of self-regulation of motivation and actions. Generally, autonomy is a central characteristic of healthy functioning and is related to a

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higher degree of well-being and satisfaction of basic psychological needs [1, 2]. Individuals experiencing a high degree of autonomous behavior perform actions in agreement with their inner values and interests [1]. Conversely, individuals with a low degree of autonomy have a higher risk of developing psychopathology like depression and anxiety.

Multiple approaches to the theoretical definition and conceptualization of autonomy are proposed; however, autonomy as a construct is still not well-defined. In a review on existing psychological theories on the definition of autonomy, Hmel & Pincus [3] described three core aspects of autonomy: autonomy as self-governance, autonomy as separation, and autonomy as vulnerability. Autonomy as self-governance implies self-regulation and self-ruling while being in meaningful relations and interactions with others. The aspect of autonomy as separation implies separation of self from others and the need to act independently. Finally, autonomy as vulnerability implies a cognitive vulnerability associated with the clinical aspects of depression. Although the three core aspects were confirmed in their structural analysis of 15 self-report scales, Hmel & Pincus [3] argued that autonomy as vulnerability did not include the essential element of "agency" and thus, could not constitute a core aspect of autonomy. Irrespectively, autonomy has been linked to depression and also anxiety in several studies [4–7], but disagreement exists as to the degree and types of autonomy that are predictive of psychiatric illnesses.

Huntington's disease (HD) is an autosomal dominantly inherited neurodegenerative disease that is characterized by a triad of symptoms, with increasing motor, cognitive, and neuropsychiatric impairments [8, 9]. Among the most prominent symptoms are chorea, dystonia and bradykinesia, psychomotor slowing, executive and social dysfunctions, as well as neuropsychiatric symptoms like depression and anxiety [9–11]. In time, the daily functioning of individuals with HD will be affected by the motor, cognitive, and neuropsychiatric symptoms, to such a degree where individuals need assistance in basic activities of daily living. These symptoms might cause diminished feelings of competence and inner resources, thereby repressing self-regulated actions and motivations. To our knowledge, no study has examined to which degree the symptoms might affect the self-perception of individuals with HD. Specifically, if these symptoms repress the autonomy of HD gene expansion carriers, to a degree that may decrease their perceived self-regulation. Such studies could contribute with information on a person's ability to cope with their disease, to preserve social relationships, and to make important life decisions and decisions of care [12, 13].

We investigated autonomy (defined as self-governance) in HD gene expansion carriers with an explorative study design. Since autonomy is often perceived as a stable personality trait in adults, it could be hypothesized that autonomy would not decrease with disease progression in HD. However, recent studies have found that the perception of self and identity is negatively affected by dementia [12, 14]. Thus, other neurodegenerative diseases might also affect the feelings of self and identity. The objective of this study was to investigate if the autonomy of individuals with HD were affected, and if there was a difference in degree of autonomy in premanifest and motor-manifest HD gene expansion carriers, using two self-report questionnaires on autonomy. Also, we examined the associations between symptoms of HD and autonomy and investigated if individuals with a low degree of autonomy had a higher risk of experiencing motor disturbances, neuropsychiatric symptoms, cognitive decline, or symptoms of apathy.

MATERIALS AND METHODS

Participants

The participants were 44 HD gene expansion carriers enrolled from the Neurogenetics Clinic, Danish Dementia Research Centre, Rigshospitalet - Blegdamsvej, Copenhagen, Denmark from year 2020-2021. All participants had previously participated in a prospective cohort study on HD at our clinic [15, 16] and were invited to participate in the current study when attending their regular assessment in the clinic. The participants were included based on the following criteria: a Unified Huntington's Disease Rating Scale-99 total motor score (UHDRS-TMS) $\leq$55 [17], a Montreal Cognitive Assessment (MoCA) score $\geq$19 [18], a Mini-Mental State Examination (MMSE) score $\geq$24 [19], and a CAG repeat length $\geq$39. Exclusion criteria were other neurological disease, ongoing alcohol- or drug abuse, or a native language other than Danish.

A classification as motor-manifest HD gene expansion carrier was given if the participants had an UHDRS-TMS>5. Contrarily, participants were classified as premanifest HD gene expansion carriers if they presented without substantial motor symptoms and had an UHDRS-TMS $\leq$5. This cut-off on the

UHDRS-TMS scale has previously been applied in the TRACK-HD study [20].

A control group of 19 at-risk individuals who had tested negative for the HD gene expansion (a CAG repeat length <30) was also included. This group was used to match the gene expansion carriers concerning the environmental and psychosocial factors that could have an impact on the results.

All participants had received genetic counselling and were informed of their genetic status prior to and independently from enrolment in this study.

Procedure and instruments

The study was approved by the Ethics Committee of the Capital Region of Denmark (H-17002606) and performed in accordance with the ethical standards of the Helsinki Declaration. Written informed consent was obtained from all participants before enrolment in the study. The participants had one visit in our clinic, where both the regular assessment and the neuropsychological assessment were performed.

Neuropsychological assessment

Participants were examined with a neuropsychological battery on self-perception and autonomy. Self-perception was assessed using a modified version of the Twenty Statements test [21], the Self-identity in Dementia Questionnaire [12], and the Tennessee Self-Concept Scale, Identity Component [22]. Here, we report only on the autonomy scales (please see description in the following).

During the assessment, participants were assessed with instruments on neuropsychiatric symptoms, cognitive status, and symptoms of apathy. The neuropsychiatric symptoms were examined using the Hamilton Depression Scale (HAM-17) [23] and the Symptom Checklist-90 Revised (SCL-90-R) [24]. The HAM-17 is a semi-structured interview on depression and depressive symptoms [23]. It contains 17 items, that are scored on either a 5-point scale (0–4) or a 3-point scale (0–2), where "0" indicates that the symptom is not present, and a higher score indicates increased severity of the symptom. The SCL-90-R is a self-report inventory with 90 items that assesses the status of one's psychological distress within the previous seven days [24]. Each item reflects one psychological symptom, and the participant must answer on a 5-point Likert scale ranging from 1 "not at all" to 5 "extremely" distressing. The raw scores were converted to T scores, normalized to a sample of nonpsychiatric Danish participants, sorted by gender [25]. Nine symptom dimensions and three global indexes are described by the SCL-90-R. Here, we used the Global Severity Index (GSI) and the dimensions Depression and Anxiety of the SCL-90-R, to describe the neuropsychiatric status of the participants.

Cognitive symptoms were assessed with the short screening test MoCA [18]. Apathy was examined using the Lille Apathy Rating Scale (LARS) [26], a standardized structured interview on symptoms of apathy. The LARS contains 33 items divided into 9 domains. The first three items are scored on a 5-point Likert scale, while item 4–33 are positively worded questions, that are answered by yes/no answers (binary scale, with an additional NA for non-applicable items). LARS yields a global score and four subscale scores (Intellectual Curiosity, Emotion, Action Initiation, and Self Awareness), where a higher score indicates a higher degree of apathy. The LARS has previously been used for examining apathy in HD [27].

Assessment of autonomy

Autonomy was assessed using two self-report questionnaires: the Autonomy-Connectedness Scale (ACS-30) [28] and the Index of Autonomous Functioning (IAF) [29]. Both scales were translated to Danish agreed upon with the authors of the original scales.

The ACS-30 scale is a self-report questionnaire on autonomy [28]. It was developed as a shorter version of the Autonomy scale [30], with a theoretical background that draws on elements from feminist theory, neo-analytical object relations theory, and attachment theory, and describes autonomy as self-governance [3]. The scale was developed for healthy subjects and has to our knowledge not previously been used in patients with neurological disorders. In the ACS-30, autonomy and connectedness is not seen as opposites on a dimension, but focuses on the subject as autonomous while being connected to others [28].

The ACS-30 consists of 30 questions that participants must answer on a 5-point Likert scale, ranging from 1 (disagree) to 5 (agree). It has a three-factor structure, where autonomy is described through three subscales: Sensitivity to Others (Sensitivity – 17 items), Capacity for Managing New Situations (Capacity – 6 items), and Self-Awareness (Self-Awareness – 7 items). Capacity does not describe

elements of self-governance, but was included because the authors found it to be a clinical relevant aspect of autonomy [28]. A higher score on each of the three subscales represents a higher degree of the trait in that subscale.

A difference between the sexes on the Sensitivity subscale, where women scored higher than men, corresponded to a large effect when examined in the original study [28]. The authors argue that this sex difference support the relevance of connectedness as a characteristic of female identity, and thus, underline the idea that connectedness is an inseparable aspect of autonomy.

The ACS-30 has been found to be a reliable instrument with sufficient convergent validity. In the Bekker & van Assen [28] study, Cronbach's alpha was reported to be 0.83, 0.82 and 0.81 for Sensitivity, Capacity, and Self-Awareness, respectively. Moderate correlation coefficients were found between the three subscales on the ACS-30 and the Occupational Self-Efficacy scale [31], the Symptom Checklist-90 [32], and Becks Depression Inventory [33]. The authors argued that these results represented initial support for the validity of the ACS-30 and that the moderate correlation coefficients indicated that there was no contamination by the clinical measures [28].

The IAF is a self-reported questionnaire on autonomy, that was developed for healthy individuals with a theoretical background in self-determination theory [29]. Self-determination theory places the definition of autonomy within the core aspect of self-governance [2, 3]. According to the self-determination theory, autonomy is described as an inner self-regulation of behavior, where an individual with a high degree of autonomous behavior perceive their actions as congruent with their self, and this is most often associated with positive outcomes like well-being and improved performance [1, 2].

The IAF includes 15 questions, which participants must answer on a 5-point Likert scale, ranging from 1 (not at all true) to 5 (completely true). Like the ACS-30, the IAF was also developed with a three-factor structure and consisted of the three subscales: Authorship/Self-congruence (5 items), Interest-taking (5 items), and Susceptibility to control (5 items). Based on the method from the original study [29], a total score was calculated, as the summed score of Authorship/Self-congruence and Interest-taking, subtracted the score of Susceptibility to control (Total IAF = Author + Interest – Control). A higher total score indicates a higher degree of autonomy.

In the original paper, the IAF was validated through several studies, that placed the IAF in a nomological net, where both convergent and divergent validity were examined with satisfactory results [29]. The IAF had meaningful correlations to measures of personality characteristics, satisfaction, and well-being outcomes, as well as other instruments that examined autonomy, like the Emotional Autonomy scale [34] and the General Causality Orientation Scale [35]. The internal reliability was examined through seven studies, with Cronbach's alpha levels between 0.81–0.83 for the Total IAF score [29]. Test-retest reliability was examined over a 6-month period and results showed high consistency across time (ICC = 0.86, $p < 0.001$). The IAF has previously been applied in a sample of patients with multiple sclerosis [36].

Statistical analyses

Group comparisons between the motor-manifest HD gene expansion carriers, the premanifest HD gene expansion carriers, and controls on the demographic variables and the basic clinical variables were performed using one-way analysis of variance (ANOVA) or the Kruskal Wallis test when the assumption of homogeneity of variances was not met. *Post hoc* comparisons were performed using Dunnett's *t*-test or pairwise comparisons. The same method was used for group comparisons of the autonomy performance scores.

Correlation analyses were applied to test the level of significance of the associations between variables with Pearson's r or Spearman's rho (for skewed distributions). To examine the associations between the basic clinical variables and autonomy in participants with a very low degree of autonomy, we calculated a 10th percentile cut-off score on the ACS-30 subscales and the Total IAF score based on the scores of the controls. The association analyses were performed in the group of motor-manifest HD gene expansion carriers with a low degree of autonomy or the entire group of motor-manifest HD gene expansion carriers depending on the number classified as below the 10th percentile cut-off score. The basic clinical information that was examined included the neuropsychiatric scale scores (the HAM-17 and the SCL-90-R GSI, Depression, and Anxiety), a motor score (the UHDRS-TMS), an apathy score (the global LARS), and a cognitive screening test (the MoCA).

For all analyses the Bonferroni-Holm correction was used to adjust the level of significance when multiple comparisons were performed. The alpha

level for significance was $p < 0.05$ (two-tailed significance).

RESULTS

Table 1 shows the demographic data and basic clinical information (the HAM-17, the SCL-90-R GSI, Depression, and Anxiety, the UHDRS-TMS, the global LARS, and the MoCA) on the HD gene expansion carriers and the controls. No significant difference in educational level or on the HAM-17 scale were found. The motor-manifest HD gene expansion carriers differed significantly from the other groups on almost all other measures (except for the educational level, the HAM-17 score, and age for the controls). The premanifest HD gene expansion carriers were significantly younger than the controls but did not differ significantly from controls on any other measure.

Table 1
Demographic data and basic clinical information on the HD gene expansion carriers and the controls. Results are presented as mean (SD), unless otherwise noted

	HD gene expansion carriers		Controls
	Premanifest HD	Motor-Manifest HD	
N	20	24	19
Sex (M/F)	11/9	17/7*	7/12
Age	39.1 (9.3)*	54.3 (11.7) †	52.7 (12.3)
Educational Level	14.4 (1.7)	13.6 (1.9)	14.7 (1.9)
UHDRS-TMS	1.7 (1.3)	23.6 (13.5)*†	1.6 (1.7)
HAM-17	2.5 (1.9)	3.4 (2.8)	3.0 (2.5)
SCL-90-R GSI	40.0 (8.0)	51.5 (9.3) *†	41.8 (10.5)
SCL-90-R Depression	42.9 (7.1)	50.9 (7.7) *†	43.5 (8.1)
SCL-90-R Anxiety	40.9 (7.0)	51.4 (9.2) *†	42.0 (7.1)
MoCA	28.5 (1.8)	26.1 (2.6)*†	28.4 (2.0)
Global LARS	–26.7 (4.4)	–23.2 (5.8)*†	–27.4 (2.5)

*Statistically significant difference from the controls ($p < 0.05$). †Statistically significant difference from the premanifest HD gene expansion carriers ($p < 0.05$). F, female; GSI, Global Severity Index; HAM-17, Hamilton Depression Scale; HD, Huntington's Disease; LARS, Lille Apathy Rating Scale; M, Male; MoCA, Montreal Cognitive Assessment; N, number of participants; SCL-90-R, Symptom Checklist-90 Revised; SD, standard deviation; TMS, Total Motor Score; UHDRS, Unified Huntington's Disease Rating Scale.

Table 2 presents the scores on the ACS-30 and the IAF as divided by groups. The premanifest and motor-manifest HD gene expansion carriers differed significantly on the Total IAF score (the motor-manifest participant scored significantly lower than the premanifest HD gene expansion carriers). The motor-manifest HD gene expansion carriers had significantly lower scores than the controls on the ACS-30 Capacity subscale, whereas the premanifest group did not differ significantly from the controls on any measure of autonomy.

The motor-manifest participants were classified as below the 10th percentile cut-off or not on the ACS-30 subscales and the Total IAF score. Table 3 shows the number and percentages of motor-manifest HD gene expansion carriers classified as having a low degree of autonomy when using the 10th percentile cut-off (a less conservative cut-off) compared to the 5th percentile cut-off which corresponds to the normally used 2 SD below the mean. Six motor-manifest HD gene expansion carriers (25%) scored below the 10th percentile the ACS-30 Sensitivity subscale. These individuals had a low degree of sensitivity to others and a low degree of autonomy. When examining if ACS-30 Sensitivity was associated with scores on the basic clinical variables, no significant correlations were found. Eight persons (33%) of the motor-manifest HD gene expansion carrier group, scored below the 10th percentile on the ACS-30 Capacity subscale, suggesting a low

Table 2
Scores on the ACS-30 and the IAF for all HD gene expansion carriers and the controls. Scores are reported as mean (SD)

	HD Gene Expansion Carriers		Controls
	Premanifest HD	Motor-Manifest HD	
N	20	24	19
ACS-30			
ACS-30 Sensitivity	54.9 (8.7)	56.8 (7.5)	57.1 (5.4)
ACS-30 Capacity	21.0 (5.6)	19.4 (5.7)*	23.2 (3.9)
ACS-30 Self-Awareness	27.0 (5.3)	25.1 (5.6)	26.8 (3.1)
IAF			
Total Score	28.3 (3.5)	24.5 (6.5)†	26.5 (4.5)

*Statistically significant difference from the controls ($p < 0.05$). ‡Statistically significant difference from the premanifest HD gene expansion carriers ($p < 0.05$). ACS-30, Autonomy-Connectedness Scale; HD, Huntington's disease; IAF, Index of Autonomous Functioning; N, number of participants.

Table 3
Frequency of the motor-manifest HD gene expansion carriers classified as below the cut-off when using the 10th percentile and 5th percentile cut-off scores

	Cut-off	
	10th percentile	5th percentile
IAF		
Total	2 (8 %)	2 (8 %)
ACS-30		
Sensitivity	6 (25 %)	1 (4 %)
Capacity	8 (33 %)	6 (25 %)
Self-Awareness	9 (38 %)	8 (33 %)

Frequency is reported as N (%). ACS-30, Autonomy-Connectedness Scale; HD, Huntington's disease; IAF, Index of Autonomous Functioning; N, number of participants.

degree of capacity for managing new situations and therefore a low degree of autonomy. A significant negative correlation between the global LARS score and the ACS-30 Capacity score was found in the entire group of motor-manifest HD gene expansion carriers ($r = -0.65$, $p = 0.001$), indicating that participants with a high capacity for managing new situations have a low degree of apathy. On the ACS-30 Self-Awareness subscale, 9 motor-manifest HD gene expansion carriers (38%) scored below the 10th percentile, suggesting a low degree of self-awareness and a low degree of autonomy. No significant correlations were found between the ACS-30 Self-Awareness subscale and the basic clinical variables in this group. For the Total IAF score, only two motor-manifest HD gene expansion carriers scored below the 10th percentile, and consequently, no association analyses were applied. There were no significantly correlated association between the basic clinical variables and the Total IAF score when examined in the entire group of the motor-manifest HD gene expansion carriers.

Figure 1 illustrates the distribution of scores on the Total IAF, the ACS-30 Capacity subscale, and the Global LARS in the three groups. As can be seen the motor-manifest HD gene expansion carriers had a higher dispersion of scores on all measures. Although the scores differ significantly from the premanifest HD gene expansion carriers on the Total IAF, the controls on the ACS-30 Capacity subscale, and both groups on the Global LARS, there was an overlap between the scores of the three groups.

A significant correlation between the ACS-30 Self-Awareness subscale and the Total IAF score was found for the motor-manifest HD gene expansion carriers (rho = 0.48, $p = 0.019$). The other ACS-30 subscales did not correlate significantly with the Total IAF score.

DISCUSSION

This study was the first study to investigate if the perception of autonomy is affected in HD. By using an exploratory study design, we examined the degree of autonomy (defined as self-governance) in premanifest and motor-manifest HD gene expansion carriers. Further, we investigated the possible associations between autonomy and basic clinical measures like motor function (the UHDRS-TMS score), neuropsychiatric symptoms (the SCL-90-R and the HAM-17 scores), cognitive status (the MoCA score), and apathy (the LARS score).

Among the motor-manifest HD gene expansion carriers, 25–38% of the participants scored substantially lower than the normal level on the ACS-30 subscales, as compared to controls. No significant associations were found between a low degree of autonomy and motor performance or neuropsychiatric and cognitive screening test, so autonomy did not seem to be associated with symptoms or progression of disease in HD. Only apathy was a relevant focus for these individuals, as a significant association was found between the ACS-30 Capacity subscale and the global LARS score. This important result demonstrates that a theoretically relevant association exists between low initiation and motivation, and low self-regulation, and it contributes impor-

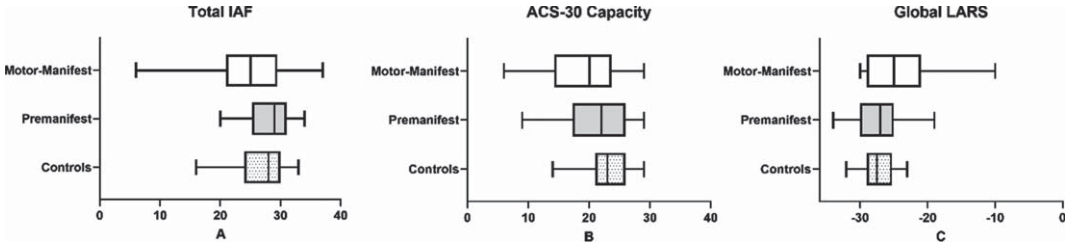

Fig. 1. Dispersion of scores for the motor-manifest HD gene expansion carriers, the premanifest HD gene expansion carriers, and the controls on the Total IAF, the ACS-30 Capacity, and the Global LARS. Error bars represents min. and max. scores.

tantly to the evidence on apathy, specifically when considering that apathetic symptoms are frequently reported in individuals with HD [37]. Interestingly, only the ACS-30 Capacity subscale was significantly associated with apathy on the LARS, the only subscale that did not describe elements of autonomy as self-governance. Instead, the ACS-30 Capacity subscale include aspects of interest in new situations, the ability to enjoy new activities, and to be adventurous. This might be more associated with the classical aspects of apathy, with diminished motivation and activity, and a lack of interest and initiative, while other aspects of autonomy like the understanding of oneself and the regulation of attitudes and opinions may not be associated with apathy to the same degree.

It should be noted that these results are not merely illustrating that HD gene expansion carriers are affected by growing up in a family with HD, since the control participants were also family members, but with a negative gene test. The results illustrate that a moderate number of HD gene expansion carriers have a substantially lower degree of autonomy, when compared to healthy family members, irrespective of environmental and psychosocial factors.

The motor-manifest HD gene expansion carriers had a significantly lower degree of autonomy compared to premanifest HD gene expansion carriers on the Total IAF, which indicates that the symptoms of HD do affect the degree of autonomy. Individuals with more advanced HD might have more diminished feelings of autonomy, and thereby more diminished feelings of self-regulation and competence as proposed by Ryan & Deci [1, 2]. The motor-manifest HD gene expansion carriers had a significantly lower capacity for managing new situations and thus autonomy on the ACS-30, when compared to controls. These results are in line with the results by Addis & Tippett [13] and Caddell & Clare [12], who reported that the perception of self and identity was negatively affected by dementia. Thus, neurodegenerative diseases can affect the individual's self-perception and the neurodegeneration of HD seem to similarly affect the self-perception of the individual with the disease. However, as seen in Fig. 1, there was a large overlap between the autonomy scores in the three groups, which oppositely suggests that the disease progression is not associated with autonomy. This suggestion was further supported by the lack of correlation between the UHDRS-TMS and the Total IAF or the ACS-30 subscales for the motor-manifest HD gene expansion carriers. Thus, the lower degree of autonomy in the motor-manifest participants might be driven by other factors than disease progression. Interestingly, the premanifest HD gene expansion carriers did not score differently on any measure of autonomy when compared to controls. Thus, autonomy does not seem to be affected in the early stages of disease, unlike other symptoms of HD, e.g., social cognition [38]. Irrespectively, the present results showed that the self-perception of autonomy in individuals with motor-manifest HD was affected to some degree. These important results should be considered when caring for individuals in more advanced stages of HD, as diminished perception of autonomy could affect the individual's ability to cope with their disease, to interact with family, friends, or professionals, or to make important decisions on care. This underlines the importance of supporting perception of autonomy throughout the disease course, e.g. by promoting a person's normal life and control in care [39].

While this study showed that autonomy was associated with apathy, it did not illustrate a significant association between autonomy and psychiatric symptoms, as was found by Bekker & van Assen [28]. This was somewhat surprising since it could be hypothesized that a low degree of autonomy could help identify people at risk for neuropsychiatric symptoms. There are several differences between the studies, but methodological differences in instruments used for examining psychiatric symptoms seem most important. While Bekker & van Assen [28] used the original SCL-90 scale, we used the revised version, where scores were normalized to a Danish sample. Moreover, this negative finding could also be caused by the relatively low number of participants in the present study. It would be interesting to investigate if an association between autonomy and psychiatric symptoms in HD could be replicated in a larger cohort.

Since we used an exploratory design, two different quantitative measures for autonomy were applied. Both the ACS-30 and the IAF defined autonomy as in the core aspect of self-governance, where actions are regulated by the self, while being in meaningful interactions with others [3]. The fact that the scales measure the same construct was supported by the significant correlation between the ACS-30 Self-Awareness subscale and the Total IAF. However, since no other subscale of the ACS-30 was significantly associated with the Total IAF, the two instruments also measure different characteristics of autonomy. Interestingly, the characterization of autonomy used in the ACS-30 seemed to be more

sensitive to the changes in individuals with HD, as a higher frequency of participants with a substantially lower autonomy was found than on the IAF scale. One explanation could be that the ACS-30 includes items on the ability to understand and feel with others (the Sensitivity subscale), which may tap abilities of theory of mind, often affected in HD [38], as well as the abilities to handle new situations (the Capacity subscale), which is associated with apathy often found in HD [37]. The IAF includes items concerning the ability to understand oneself and one's actions, which has not previously been investigated in HD.

One substantial limitation of the present study is the low number of participants included. As this was an exploratory study, we did not include a power analysis. Therefore, it remains unknown whether the missing difference on two of the ACS-30 subscales are genuine or an artefact caused by the low number of participants. However, the results should be seen as an attempt to explore the possible neurodegenerative effect on the self-perception of autonomy by HD and not a final measure of effect. Another limitation concerns the use of self-report measures in studies of HD, as individuals with HD might have decreased insight into their symptoms, proposedly more frequently in more severe stages of disease [40, 41]. The autonomy scales used in the present study were both rated on a 5-point Likert scale, where diminished insight might inhibit ratings in the lowest or highest ends of the scale, thereby increasing the probability of answering in the middle of the scale. It cannot be ruled out that the missing difference between the groups on the two ACS-30 subscales might have been affected by this. Moreover, as autonomy is a phenomenological construct, investigation of autonomy using quantitative rating scales should not stand alone, but in this study, we investigated autonomy with this method in an attempt to incapsulate this complex phenomenon and to explore if the perception of autonomy in individuals with HD was affected.

In conclusion, this study is the first to investigate changes in the perception of self and autonomy in HD gene expansion carriers. Using quantitative scales previously applied in other diseases we found that 25–38% of the motor-manifest HD gene expansion carriers had a degree of autonomy that was substantially lower than the level of gene negative family controls, and these individuals might be at risk of having apathetic symptoms as well. Contrarily, the autonomy of the premanifest HD gene expansion carriers were not affected by the disease, as they did not differ significantly from the controls. The current results should be interpreted in the light of the conceptualization of autonomy as self-governance. While self-governance has gained theoretical foothold specifically in newer studies, other conceptualizations of autonomy exist and might have generated different results. As an example, autonomy defined as vulnerability has been associated with depression in previous studies [6, 7]. Nevertheless, the current results illustrate that changes in autonomy can occur in HD and underline the importance of maintaining patient autonomy and involvement when caring for individuals with HD.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

[1] Ryan RM, Deci EL. Self-regulation and the problem of human autonomy: Does psychology need choice, self-determination, and will? J Pers. 2006;74(6):1557-86.

[2] Ryan RM, Deci EL. Self-determination theory and the facilitation of intrinsic motivation, social development, and well-being. Am Psychol. 2000;55(1):68-78.

[3] Hmel BA, Pincus AL. The meaning of autonomy: On and beyond the interpersonal circumplex. J Pers. 2002;70(3):277-310.

[4] Rutten EAP, Bachrach N, van Balkom AJLM, Braeken J, Ouwens MA, Bekker MHJ. Anxiety, depression and autonomy–connectedness: The mediating role of alexithymia and assertiveness. Psychol Psychother. 2016;89(4):385-401.

[5] Bekker MHJ, Belt U. The role of autonomy-connectedness in depression and anxiety. Depress Anxiety. 2006;23:274-80.

[6] Bieling PJ, Alden LE. Sociotropy, autonomy, and the interpersonal model of depression: An integration. Cognit Ther Res. 2001;25(2):167-84.

[7] Marfoli A, Viglia F, Di Consiglio M, Merola S, Sdoia S, Couyoumdjian A. Anaclitic-sociotropic and introjective-autonomic personality dimensions and depressive symptoms: A systematic review. Ann Gen Psychiatry. 2021;20(1):1-30.

[8] Walker FO. Huntington's disease. Lancet. 2007;369:218-28.
[9] McColgan P, Tabrizi SJ. Huntington's disease: A clinical review. Eur J Neurol. 2018;25(1):24-34.
[10] Paoli RA, Botturi A, Ciammola A, Silani V, Prunas C, Lucchiari C, et al. Neuropsychiatric burden in huntington's disease. Brain Sci. 2017;7(6):1-15.
[11] Snowden JS. The neuropsychology of Huntington's disease. Arch Clin Neuropsychol. 2017;32(7):876-87.
[12] Caddell LS, Clare L. The impact of dementia on self and identity: A systematic review. Clin Psychol Rev. 2010;30(1):113-26.
[13] Caddell LS, Clare L. How does identity relate to cognition and functional abilities in early-stage dementia? Aging Neuropsychol Cogn. 2013;20(1):1-21.
[14] Addis DR, Tippett LJ. Memory of myself: Autobiographical memory and identity in Alzheimer's disease. Memory. 2004;12(1):56-74.
[15] Vinther-Jensen T, Larsen IU, Hjermind LE, Budtz-Jørgensen E, Nielsen TT, Nørremølle A, et al. A clinical classification acknowledging neuropsychiatric and cognitive impairment in Huntington's disease. Orphanet J Rare Dis. 2014;9(114):1-9.
[16] Hellem MNN, Hendel RK, Vinther-Jensen T, Larsen IU, Nielsen TT, Hjermind LE, et al. Endophenotypical drift in Huntington's disease: A 5-year follow-up study. Orphanet J Rare Dis. 2021;16(1):340.
[17] Huntington's Study Group. Unified Huntington's Disease Rating Scale: Reliability and consistency. Mov Disord. 1996;11(2):136-42.
[18] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment (MoCA): A brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53(4):695-9.
[19] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98.
[20] Tabrizi SJ, Langbehn DR, Leavitt BR, Roos RA, Durr A, Craufurd D, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. Lancet Neurol. 2009;8(9):791-801.
[21] Watkins D, Yau J, Dahlin B, Wondimu H. The twenty statements test. J Cross Cult Psychol. 1997;28(5):626-33.
[22] Fitts WH, Warren WL. Tennessee Self-Concept Scale, Second Edition (TSCS:2) [Manual]. 2nd ed. Fitts WH, Warren WL, editors. Torrance, CA: Western Psychological Services; 1996, pp. 1-118.
[23] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.
[24] Derogatis LR. SCL-90-R, Vejledning til administration og scoring, Dansk Version. Derogatis LR, editor. Pearson; 2009, pp. 3-71.
[25] Olsen LR, Mortensen EL, Bech P. The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample. Acta Psychiatr Scand. 2004;110(3):225-9.
[26] Sockeel P, Dujardin K, Devos D, Denève C, Destée A, Defebvre L. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: Validation in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006;77(5):579-84.
[27] Hendel RK, Hellem MNN, Hjermind LE, Nielsen JE, Vogel A. Intellectual curiosity and action initiation are subtypes of apathy affected in Huntington disease gene expansion carriers. Cogn Behav Neurol. 2021;34(4):295-302.
[28] Bekker MHJ, van Assen MALM. A short form of the autonomy scale: Properties of the autonomy–connectedness scale (ACS–30). J Pers Assess. 2006;86(1):51-60.
[29] Weinstein N, Przybylski AK, Ryan RM. The index of autonomous functioning: Development of a scale of human autonomy. J Res Pers. 2012;46(4):397-413.
[30] Bekker MHJ. The development of an Autonomy scale based on recent insights into gender identity. Eur J Pers. 1993;7(3):177-94.
[31] Schyns B, von Collani G. A new occupational self-efficacy scale and its relation to personality constructs and organizational variables. Eur J Work Organ Psychol. 2002;11(2):219-41.
[32] Derogatis LR, Lipman RS, Covi L. SCL-90: An outpatient psychiatric rating scale - preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.
[33] Beck AT, Baemesderfer A. Assessment of depression: The Depression inventory. Psychol Meas Psychopharmacol. 1974;7:151-69.
[34] Steinberg L, Silverberg SB. The vicissitudes of autonomy in early adolescence. Child Dev. 1986;57(4):841-51.
[35] Deci EL, Ryan RM. The general causality orientations scale: Self-determination in personality. J Res Pers. 1985;19(2):109-34.
[36] Barta T, Kiropoulos L. The mediating role of stigma, internalized shame, and autonomous motivation in the relationship between depression, anxiety, and psychological help-seeking attitudes in multiple sclerosis. Int J Behav Med. 2022; doi: 10.1007/s12529-022-10078-6.
[37] van Duijn E, Kingma EM, van der Mast RC. Psychopathology in verified Huntington's disease gene carriers. J Neuropsychiatry Clin Neurosci. 2007;19(4):441-8.
[38] Bora E, Velakoulis D, Walterfang M. Social cognition in Huntington's disease: A meta-analysis. Behav Brain Res. 2016;297:131-40.
[39] Houska A, Loucka M. Patient's autonomy at the end of life, a critical review. J Pain Symptom Manage. 2019;57(4):835-45.
[40] Sitek EJ, Thompson JC, Craufurd D, Snowden JS. Unawareness of deficits in Huntington's disease. J Huntingtons Dis. 2014;3(2):125-35.
[41] McCusker E, Loy CT. The many facets of unawareness in Huntington disease. Tremor Other Hyperkinet Mov (N Y). 2014;2014(1):1-8.

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