Univerzita Karlova

1. lékařská fakulta

Doktorské studijní programy v biomedicíně

Studijní program: Neurovědy

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Clinical Applicability of Cognitive Testing in Huntington Disease

Využití kognitivích testů u Huntingtonovy nemoci v klinické praxi

Disertační práce

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Praha, 2022

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Identifikační záznam:

MÜHLBÄCK, Alzbeta Clinical applicability of cognitive testing in Huntington Disease [Využití kognitivích testů u Huntingtonovy nemoci v klinické praxi]. Praha, 2022. Počet stran: 167. Disertační práce (Ph.D.). Univerzita Karlova v Praze, 1. lékařská fakulta, Neurologická klinika. Školitel: doc. MUDr. Jiří Klempíř, Ph.D.

Acknowledgement

I would like to express my deep gratitude to assoc. Prof. Jiří Klempíř, my research supervisor, for his patient guidance, enthusiastic encouragement and valuable critiques of this research work and his advice and assistance in keeping my progress on schedule. I would also like to thank Prof. Jan Roth, Prof. Matthias Dose, Prof. G. Bernhard Landwehrmeyer and Prof. Jan Motlik for their valuable advice and support. My thanks are also extended to assoc. Prof. Ondrej Bezdicek and Josef Mana for their help in the data analysis and Michael Wallner for supporting this study's normative calculator and technical aspects.

I would also like to extend my thanks to the medical director Prof. Peter Brieger for providing me with resources for this project and as well and my colleagues Rainer Hoffmann, Rudolf Dengler, Jeanette Glasl, Angelika Hacker, Michael Bachmaier at the Huntington Center South in Taufkirchen and the entire department for their support. I would also like to thank my colleagues and friends Viera Bregulla, Katarina Hubcikova, Katrin Barth, Wiebke Frank, Olga Klempirova and Katrin Lindenberg for their constant support.

Furthermore, I would like to thank all the patients and their families involved in this research to make this study possible. My graduate thanks are also extended to patients' organisations and Astri Arnesen, Bea de Schepper and Danuta Lis for their constant support of our international projects.

This project was conducted within the framework of the EU Joint Programme Neurodegenerative Disease Research (JPND).

Finally, I would like to thank my husband, my sister and my family, who have always believed in me, listened to me and supported me in hard times, especially my mother and father, who have supported me at all stages of my career from a very young age until today.

Abstract

Introduction: Huntington disease (HD) is an autosomal dominant neurodegenerative disorder manifested by motor, behavioural and cognitive deficits with fatal consequences.

Aims: This study aims to validate the psychometric properties of a standard cognitive battery used in HD and establish language-specific normative values.

Methods: In the first study, cognitive performance was compared in 106 patients at different stages of HD and 100 healthy controls matched for age, sex and education. The neuropsychological battery included the Symbol Digit Modalities Test, Stroop Word Reading Test, Stroop Colour Naming Test, Stroop Interference Test, Trail Making Test-A and B, Category and Letter Verbal Fluency. In addition, patients were comprehensively assessed for motor and functional status.

In the second study, the cognitive performance of 3,267 healthy subjects was assessed. The work focused on the stratification of cognitive performance concerning age, gender, language and level of education. Another aim was to establish the language-specific normative values and implement a web-based normative calculator to assess the degree of cognitive deficit in different languages (English, German, Spanish, Italian, Polish, French, Dutch and Danish).

Results: In the first study, analysis of variance showed that healthy controls performed significantly better than patients on all cognitive tests. Cognitive performance was correlated with motor and functional impairment ($p < 0.001$) independent of age and disease duration.

A normative study showed a significant non-linear decline in cognitive performance with advancing age in healthy subjects. Cognitive performance in all tests was significantly better in subjects who had attained higher education levels. In addition, language-related differences in cognitive performance were found in all tests. In terms of gender, there was a trend towards better performance on the SDMT for females.

Conclusion: The results of both studies provide normative data for a specific cognitive battery stratified by age, education, gender and language to be used in the field of HD and other neurodegenerative diseases. The normative values obtained were used to create a freely available web-based calculator that allows for use in clinical and research practice.

Keywords: Huntington disease, Unified Huntington's Disease Rating Scale, neuropsychological test battery, cognitive performance, normative data, normative calculator.

Abstrakt

Úvod: Huntingtonova nemoc (HN) je dědičné neurodegenerativní onemocnění projevující se poruchami hybnosti, chování a kognitivním deficitem s fatálními následky.

Cíle: Cílem této studie bylo ověřit psychometrické vlastnosti standardní kognitivní baterie používané u HN a stanovit jazykově specifické normativní hodnoty.

Soubor a metodika: V první studii byl porovnáván kognitivní výkon u 106 pacientů v různých stádiích HN a u 100 zdravých kontrol párovaných podle věku, pohlaví a vzdělání. Neuropsychologická baterie zahrnovala Test modalit čísel a symbolů (SDMT), Stroopův test, Test cesty, kategoriální a fonemickou verbální fluenci. U pacientů byl navíc komplexně hodnocen motorický a funkční stav.

Ve druhé studii byl hodnocen kognitivní výkon 3 267 zdravých osob. Práce byla zaměřena na stratifikaci kognitivního výkonu v souvislosti s věkem, pohlavím, rodným jazykem a vzděláním. Dalším cílem bylo na základě získaných dat vytvořit normativní kalkulátor pro hodnocení míry kognitivního deficitu v různých jazycích (angličtina, němčina, španělština, italština, polština, francouzština, nizozemština, dánština).

Výsledky: V první studii analýza rozptylu ukázala, že zdravé kontroly dosahovaly významně lepších výsledků než pacienti. Kognitivní výkon koreloval s motorickým a funkčním postižením ($p < 0,001$) nezávisle na věku a délce trvání onemocnění.

Normativní studie prokázala významný nelineární pokles kognitivního výkonu s postupujícím věkem u zdravých osob. Kognitivní výkon ve všech testech byl významně lepší u lidí, kteří dosáhli vyššího vzdělání. Kromě toho byly ve všech testech zjištěny jazykově podmíněné rozdíly v kognitivní výkonu. Z hlediska pohlaví byl zaznemenán u žen trend k lepšímu výkonu v SDMT.

Závěr: Výsledky obou studií poskytují normativní data pro kognitivní baterii specifickou pro HN, která jsou stratifikovaná podle věku, vzdělání, pohlaví a jazyka. Získané normativní hodnoty byly využity pro vytvoření volně přístupného webového kalkulátoru, který umožňuje využití v klinické i výzkumné praxi.

Klíčová slova: Huntingtonova nemoc, Jednotná škála Huntingtonovy nemoci, neuropsychologická testová baterie, kognitivní výkon, normativní data, normativní kalkulačka

Abbreviations

HD	Huntington's disease
AChE	Acetyl-Choline-Esterase
AD	Alzheimer's disease
AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid
APA	American Psychiatric Association
AUC	Area Under the Curve
BDNF	Brain-derived Neurotrophic Factor
Ca	Calcium
CAG	trinucleotide Cytosis-Adenosin-Guanine
CFT	Categorial Fluency Test
ChAT	Choline Acetyltrans-Transferase
CJD	Creutzfeld-Jakob disease
CSF	Cerebrospinal Fluid
CNS	Central Nervous System
CPN	Cortical Pyramidal Neurons
DA	Dopamine
DA1R	Dopanime Receptor 1
DA2R	Dopanime Receptor 2
DA5R	Dopanime Receptor 5
DNA	Deoxyribonucleic Acid
DSM-IV	Diagnostic and Statistical Manual of Mental disorders, fourth edition
DSM-V	Diagnostic and Statistical Manual of Mental disorders, fifth edition
DRPLA	Dentato-Rubro-Pallido-Luysian Atrophy
EGR1	Early Growth Response 1 Factor
ENK	Enkephaline
FAS	Function Assessment Scale
FAN1	Fanconi Anemia Associated Endonuclease
fMRI	Functional Magnetic Resonance Imaging
FTD	Frontotemporal Dementia
GABA	Gamma-Aminobutyric Acid
GAD2	Glutamate decarboxylase
GWAS	Genome-Wide Association Study
HAP40	Huntingtin-Associated Protein 40
HD1	HD-like Syndrome Type 1
HD2	HD-like Syndrome Type 2
HD4	HD-like Syndrome Type 4
HDGECs	HD gene-expansion carriers
HEAT	acronym for four proteins including huntingtin, elongation factor 3, protein phosphatase 2A, and target of rapamy cin 1 (TOR1)
HECT	Homologous to the E6-AP Carboxyl Terminus
HTT	Huntingtin Gene
HTT	Huntigntin Protein
IS	Independence Scale
JHD	Juvenile Huntington Disease
LFT	Letter Fluency Test
MCI	Mild Cognitive Impairment
Met-Enk	Met-Enkephalin
mHTT	mutant huntingtin
NMDA	N-methyl-D-aspartate

MMSE	Mini Mental Status Examination
MOR	μ-Opioid Receptor
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSN	Medium Spiny Neurons
MTMR10	Myotubularin related protein 10
OCB	Obsessive Compulsive Behaviour
PBA	Problem Behavior Assessment
PB	Perserverative Behaviours
PD	Parkinsonian Disorders
PDE10A	Phosphodiesterase 10A
PET	Positron Emission Tomography
PPI	Protein–Protein Interaction
polyQ	polyglutamine
p53	p53 Protein
PSP	Progressive Supranuclear Palsy
ROC	Receiver Operating Characteristic
RRM2B	a subunit of DNA damage p53-inducible ribonucleotide reductase M2B
SWRT	Stroop Word Reading Test
SCNT	Stroop Colour Naming Tast
SIT	Stroop Interference Test
SCA	Spinocerebellar Ataxia
SST	Somatostatin
SSRI	Selective Serotonin Reuptake Inhibitors
SNRI	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)
SP	Substance P
TFC	Total Function Capacity
TMS	Total Motor Score
TMT-A	Trail Making Test A
TMT-B	Trail Making Test B
URB5	an HECT domain E3 ubiquitin protein ligase
UHDRS	United Huntington Disease Rating Scale
USA	United States of America
Q	glutamine
wtHTT	wild-type huntingtin

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I. Introduction

1. Historical Perspective of Huntington Disease

1.1. Origin and Development of the Term “Chorea”

Chorea is defined as rapid, irregular, and random movements of various body parts, usually with an acral predominance. The term chorea originates from Greek and refers to dancing (choreia, choros). Latin also uses the term chorus or chorea for a dance. Theophrastus Bombast von Hohenheim, called Paracelsus (1493-1541), used the term chorea on two different occasions concerning organic diseases - chorea naturalis - and in a non-organic (spiritual) aetiology - chorea lasciva (Stevens, 1972). The description of the chorea syndrome goes back to the Middle Ages, referring to dancing mania or St. Vitus' dance in the religion, e.g. after the great plague epidemic in Aachen, for healing, it was advised to worship various saints. Sydenham (1624-1689) was the first to give a comprehensive clinical description of choreatic movements and noted their occurrence in children. Unfortunately, however, he referred to chorea in children as "dancing mania", this led to a number of misunderstandings, which is why the term chorea minor was later used for Sydenham's chorea (rheumatic chorea, chorea mollis) in children and as chorea maior for St Vitus' dance (Eftychiadis, 2001). Today, the term chorea maior is used exclusively in connection with Huntington chorea.

1.2. History of Huntington Disease

The name Huntington disease (HD) is taken from the American physician George Huntington, who published a paper in 1872 that established the hereditary nature of the disease (Huntington, 1872). George Huntington wrote this work when he was 22 years old, a year after graduating from Columbia University Medical School in New York (Heathfield, 1973). The manuscript describes the work of his father, George Lee Huntington (1811-1881) and his grandfather, Abel Huntington (1778-1858), both were physicians and worked in their family practice (Stevenson, 1934). George Huntington summarised the longitudinal observations, the notes from the patient files of the affected persons occurring in several generations in two families in East Hampton on Long Island in his manuscript (Wexler et al., 2016). Although it was not the earliest medical account of HD, it was the most comprehensive description and led to its recognition worldwide. In 1874, the work was

cited by neuropathologist Camillo Golgi when he described the pathological changes in the cortex and striatum of the 42-year-old patient with chorea (Golgi, 1874).

Although, in early 1841, Dr Charles Oscar Waters from New York wrote a letter for the first edition of The Practice of Medicine, compiled by Dr Robley Dunglison, describing a disorder known popularly as the ''magrums'', meaning ''fidgets'' in Dutch (Waters, 1842). He gave a concise account of a syndrome likely to be HD, describing a progressive character in a combination of motor and cognitive decline as well as the hereditary nature of the condition (Waters, 1842, Vale and Cardoso, 2015).

Additionally, William Osler contributes tremendously to the neurology field as he offers a valuable resource by introducing Huntington´s manuscript ''On Chorea'' in a relatively unbiased and balanced perspective (Goetz, 2000). Although Osler made numerous seminal neurological contributions, he never considered himself a neurologist (Goetz, 2000).

The first European physician to describe HD was Lund in the county Sørlandet in Norway in 1860, who referred to chorea as St Vitus' dance and illustrated the typical features of the disease using patient records (Lund, 1860). However, with the development of neurology as a medical speciality in the 1880s and the growing number of patients in psychiatric and neurological hospitals with chorea symptomatology, clinicians began to report similar cases with increasing frequency. A young physician from the medical clinic in Heidelberg, Hoffmann describes in 1888 in his work on ''chorea heriditaria'' several case reports of chorea patients with a chronic and incurable course leading to death with palsies and mental weakness. He provided a detailed description of the progression of the disease and the pedigree analysis and the onset of the first symptoms in children and adolescents, which lead to death in the second decade of life (Hoffmann, 1888). Hoffmann also described the late onset of the disease in the sixth and seventh decades of life (Hoffmann, 1888). In summarising his work, he suggested remaining with the fact that chorea heriditaria occurs in most cases between 30 and 40 years of age. However, the cases with early onset in childhood and adolescence and later may occur. The description of Hoffmann introduces the terminology of the Juvenile Huntington Disease (JHD) and Late-Onset HD (Hoffmann, 1888).

While neurologists referred to Huntington disease as a neurological disease, many more psychiatrists than neurologists encountered such patients, as the psychiatric abnormalities were already proven to be severe in the course of the disease. In these times, the physicians referred to this disorder as chorea heriditaria, choreic dementia, dementia choreica, chronic progressive chorea due to typical features such as heredity condition with severe psychiatric deficits. However, Chorea Huntington soon replaced all of this terminology (Wexler, 2008).

1.3. Hereditary Dimension of Huntington Disease – Shadow Years

With the rediscovery of Mendel's laws in 1900 (Dijk and Ellis, 2016), the hereditary dimension of Huntington disease and its specific autosomal dominant mode of inheritance receive increased attention not only from clinicians but also from biologists and researchers studying Mendelian inheritance in general (Harper, 2002). When eugenics leader Davenport conducted the first large-scale pedigree study of Huntington Chorea families, it involved 962 individuals in the USA (Davenport, 1916). This controversial paper with the title "Huntington's Chorea in Relation to Heredity and Eugenics" from 1916 was cited for years (Davenport, 1916). Although it was a methodologically inaccurate study, it supported Davenport's extreme eugenic views; and help to spread the idea of sterilization as a recommended measure and laid the foundation for later claims about Huntington and stigmatisations such as criminality and violence (Wexler, 2008). It took until the late 1960s for Hans and Gilmore, and later Wexler, to demonstrate that these pedigrees were constructed with unreliable data and methodological errors (Hans and Gilmore, 1969, Wexler et al., 2016). From the 1920s to the 1940s, it was a dark chapter for those suffering from HD or other genetic diseases. In 1927, the Supreme Court upheld a program of sterilisation of the mentally disabled in Virginia. In 1935, a committee of the American Neurological Association defended sterilisation with the consent of the patient or their caregivers and called for restrictions on marriage for conditions like HD (Harper, 2002). The same development in parallel occurred in Europe, starting in 1933 in several European countries, especially with National Socialism in Germany. The establishment of the eugenic programs that led to death for the people with genetic and other neurological and psychiatric disorders and the other measures were introduced involving sterilisation for the people affected with a genetic disorder, such as HD (Hanauske-Abel, 1996).

1.4. New Area of Huntington Disease – Patients' Initiatives

However, by the 1970s, against a backdrop of civil rights, the cultural landscape and community attitudes towards HD had changed. Many initiatives worldwide were taking place to improve care for Huntington families. One of the most important ambassadors for HD was Marjorie Guthrie, the widow of the songwriter and singer Woody Guthrie, who died of Huntington disease in 1967, and who provided the decisive impulse for the foundation of the first patient advocacy organisations (Arévalo et al., 2001). In further steps, associations and patient advocacy groups were founded in many countries in the late 1960s and 1970s. Based on the initiative of Majorie Guthrie in 1976 and 1977, the first public hearings in the congress in the USA were held to respond to the demands of families affected by HD (Arévalo et al., 2001). This contributed to a collaborative project focusing on

a unique group of Huntington affected families in Venezuela. They had already been identified in the 1950s by a local doctor Americo Negrette, author of the first monograph to be published on Huntington disease (Negrette, 1963, Moscovich et al., 2011). Under the leadership of Nancy Wexler in 1983, the identification of the genetic marker for Huntington disease was successful (Gusella et al., 1983). The new technology made it possible to study the marker for the first time and determine whether individuals were at risk for Huntington disease, whether they carried the abnormal variant of the gene and would therefore develop symptoms. The Huntington's Disease Collaborative Research Group was formed by Nancy Wexler at the same time as the Hereditary Disease Foundation (Wexler, 1995). After ten hard years of work, the group collectively announced the identification of the abnormal Huntington gene (Huntington's disease Collaborative Research, 1993).

2. Epidemiology of Huntington Disease

2.1. Prevalence of Huntington Disease

Reviews of the epidemiology of HD indicate that the worldwide prevalence of the disease varies in different areas. The recent study by Rawlins showed that the worldwide prevalence of HD shows more than tenfold patterns of variation across regions (Rawlins et al., 2016), which is also consistent with the findings of previous studies. The Maracaibo region of Venezuela has the highest reported worldwide prevalence of HD, with 700 per 100,000 (Rawlins et al., 2016). The Spanish colonised Venezuela in the 16th century; thus, the origins of HD in Venezuela can be traced back to Europe (Avila-Giron, 1973). The low prevalence rates among blacks in South Africa (Hayden et al., 1980) and Zimbabwe, about 0.48-1.84 per 100,000 (Scrimgeour and Pfumojena, 1992), may be due to weak case detection in communities with limited health services.

In contrast, Folstein et al. reported prevalence in blacks of 6.37 per 100,000 and whites of 4.79 per 100,000 in the USA (Folstein et al., 1987, Pringsheim et al., 2012). The low prevalence rates of HD in Asian countries such as Hong Kong, Japan and Taiwan are very unlikely due to poor case detection or inadequate diagnosis, as these countries have high levels of health care. Since 1995, genetic testing has been routinely used in Asian countries (Hong Kong, Japan, South Korea and Taiwan), and the average prevalence rate remains by 0.42 per 100,000 (Rawlins et al., 2016). The average prevalence rate for the same period among predominantly Caucasian populations (in Australia, Western Europe, including the UK and North America) was 9.71 per 100,000 (Xu and Wu, 2015). The

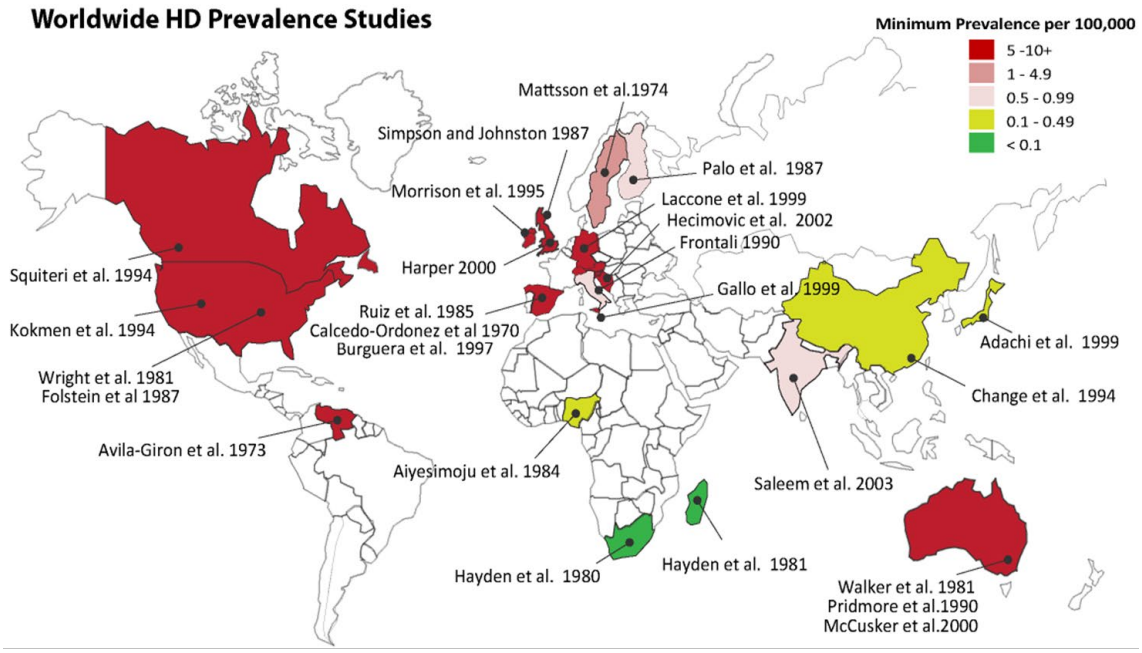
different haplotypes between East Asians and Europeans may be associated with different mutation rates (Warby et al., 2011). Generally, the highest prevalence rates are reported for Western populations from Europe, where the minimum prevalence is higher than 5 per 100,000 (Warby et al., 2011). There are also differences among different regions in Europe, with a low prevalence of 2.12 per 100,000 in Finland (Sipilä et al., 2015) and a higher prevalence of 6,18 per 100,000 in the UK (Rawlins et al., 2016). For more information on the prevalence, differences see Table 1.

Region	Number of studies in estimates of rate ratios	Study years (range)	Average prevalence per 100,000 (95% CIs)	Trend (%) by decade
Asia	7	1957–2013	0.40 (0.36–0.44)	8.9 (–2.24 to +23.8)
Central and Eastern Europe	8	1981–2008	2.17 (1.95–2.41)	15.4 (2.70 to +38.6)
North America	6	1950–2012	7.33 (6.94–7.74)	20.1 (+18.1 to 22.1)
Oceania	8	1981–2008	5.63 (5.61–6.25)	15.4 (+11.6 to +19.3)
United Kingdom	19	1950–2010	6.68 (6.40–6.97)	15.5 (+11.3 to +18.0)
Western Europe	27	1930–2013	3.60 (3.50–3.69)	16.5 (+14.9 to +18.6)

Table 1 Prevalence rate ratios in different world regions
The prevalence values in the table were adopted from Rawlins et al. (2006).

2.2. Future Prevalence Estimation

The estimated prevalence rate found was 10.85 per 100,000 in Italy, remarkably higher than that previously described before the gene test analysis was available and expected to increase an additional 17% by 2030 because of Italian population ageing (Squitieri et al., 2016). These findings of Squitieri are in line with Rawlings et al. showing that apparent prevalence rates of HD in Australia (between 1954 and 1996), North America (between 1950 and 2012), the UK (between 1950 and 2010) and other Western European countries (between 1930 and 2007) have increased by approximately 15-20% per decade (Rawlins et al., 2016). Further studies also indicate a high prevalence of individuals carrying an intermediate allele with prolonged CAG repeats in the general population. Moreover, a substantially more significant proportion of individuals than previously estimated may be at risk of developing HD later in life or bearing children with a de novo mutation (Gardiner et al., 2019).



Courtesy of M.Hayden

Figure 1: Worldwide estimates of the prevalence of HD
Overall, the prevalence of HD is much higher in European populations than in East Asia. The average minimum prevalence is shown. Available prevalence studies occurring before identifying the HD gene in 1993 could underestimate the true prevalence of HD. Many African studies have small sample sizes, and the HD diagnosis has not been confirmed by molecular testing (Warby et al., 2011).

3. Genetics of Huntington Disease

3.1. Huntingtin Gene

With the introduction of molecular biology techniques, a link HD and chromosome 4 was established in 1983 (Gusella et al., 1983). Ten years later, the responsible gene was identified, making an unstable and dynamic pathologic expansion of the cytosine-adenine-guanine (CAG) repeat within the first exon of the gene huntingtin (HTT, OMIM 613004) on the short arm of chromosome 4p16.3, responsible for HD (Huntington's disease Collaborative Research, 1993). The extended CAG tract is the trigger for the development of HD. Its length is a primary determinant for initiating the pathogenic process leading to conversion and manifest disease (Snell et al., 1993), whereby conversion refers to the appearance of the motor diagnostic signs. However, subtle behavioural changes may occur over the years before manifestation (Paulsen et al., 2017).

As already mentioned, the *HTT* gene consists of a chain of numerous CAG repeats, and a single CAG encodes the amino acid glutamine (referred to as Q). A sequence of several glutamine units is

referred to as a polyglutamine (polyQ - meaning repeating glutamine) tract (Gusella and Macdonald, 2000); for an overview, see Figure 2. HD also belongs to the polyglutamine (poly Q) disorders (Paulson, 2018). Including also spinocerebellar ataxia (SCA - 1, 2, 3, 6, 7, 8, 12, 17), dentato-rubro-pallido-luysian atrophy (DRPLA) and spinal and bulbar muscular atrophy (SBMA) (Lizuka et al., 1984). Description of the entities to be found in section 8.4. All polyQ disorders share the features of being autosomal dominant and causing disease when the number of CAG repeats crosses a particular number of a polyQ tract expansion and lead to protein misfolding and subsequent deposition of protein aggregates in neurons (Paulson, 2018). Beyond polyQ diseases, several other diseases are caused by triplet repeat, and these include autosomal recessive inherited fragile X syndrome (CGG repeat and Friedreich ataxia (GAA repeat), an autosomal dominant inherited myotonic dystrophy (CTG repeat) (Budworth and McMurray, 2013).

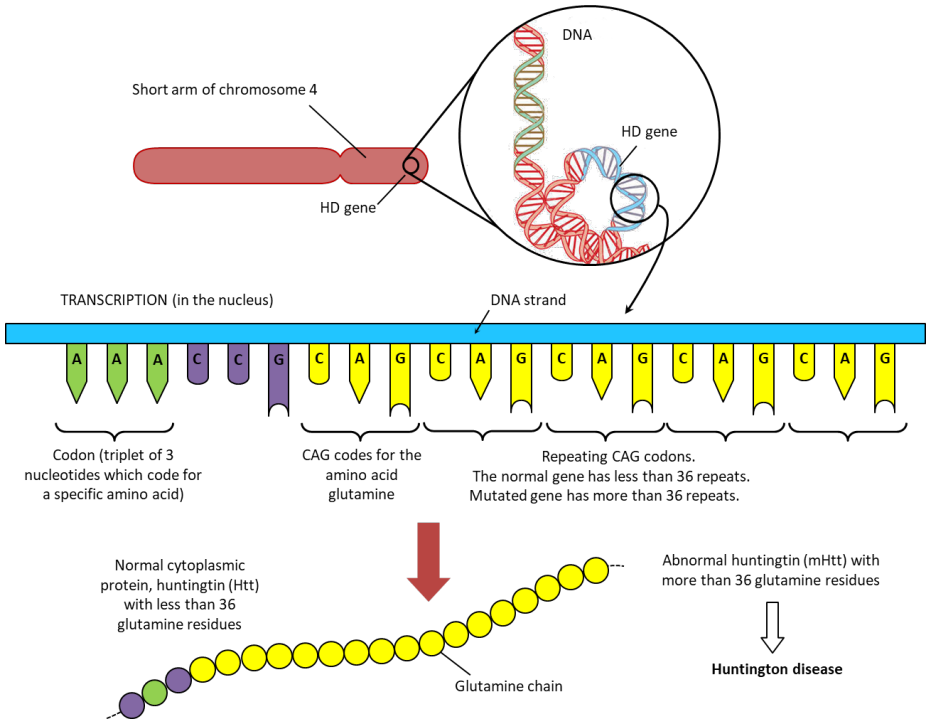


Figure 2: Huntingtin gene structure and genetic mechanism
Hunting Gene (HTT) consist of the cytosine-adenine-guanine (CAG) repeat within the first exon of the gene Huntingtin on chromosome 4, and CAG codes form a glutamine chain (PolyQ) translated into the Huntingtin Protein (HTT). The extended CAG tract (more than 36) is the primary determinant leading to HD (Huntington's disease Collaborative Research, 1993).

3.2. CAG Repeat Length

Early studies involving the analyses of the number of CAG repeats showed that the CAG tract in the *HTT* gene is polymorphic in the general population, with the normal range of repeat numbers varying from 9 to 11 at the low end and 34–37 at the high end (with an average of 17–20) (Gusella

and MacDonald, 1995). The CAG repeat lengths longer than 37 are associated with HD (Read, 1993). Subsequent studies involving large cohorts of individuals who carried between 30 and 40 CAG repeats in the *HTT* gene further refined this concept. They indicated that repeats up to 35 in length do not cause HD and that repeat lengths between 36 and 39 are associated with reduced penetrance, meaning that, within this range, some individuals develop HD within their lifetime. In contrast, others do not (Rubinsztein et al., 1996).

The number of repeats in *HTT* is inversely associated with disease onset, such that the greater the number, the earlier the onset (Snell et al., 1993, Kieburtz et al., 1994). The onset of the disease is defined as the manifestation of significant motor or neurologic symptoms and occurs on average around 40 (Roos, 2010). The CAG length is also associated with the clinical progression. Individuals with shorter CAG expansions appear to have a better prognosis(Rosenblatt et al., 2006). Figure 3 shows the variations for the onset of the disease, indicating the differences from 10 to 15 years between individuals with the same CAG length (Gusella and Macdonald, 2009). The number of CAG repeats within the normal allele does not influence the age of onset in Huntington disease (Klempíř et al., 2011). The number of CAG repeats within the HTT gene varies from 6 to 35 in the general population (Nopoulos, 2016). With less than 27 repeats, no manifestation of HD is expected, and the gene is stable upon transmission.

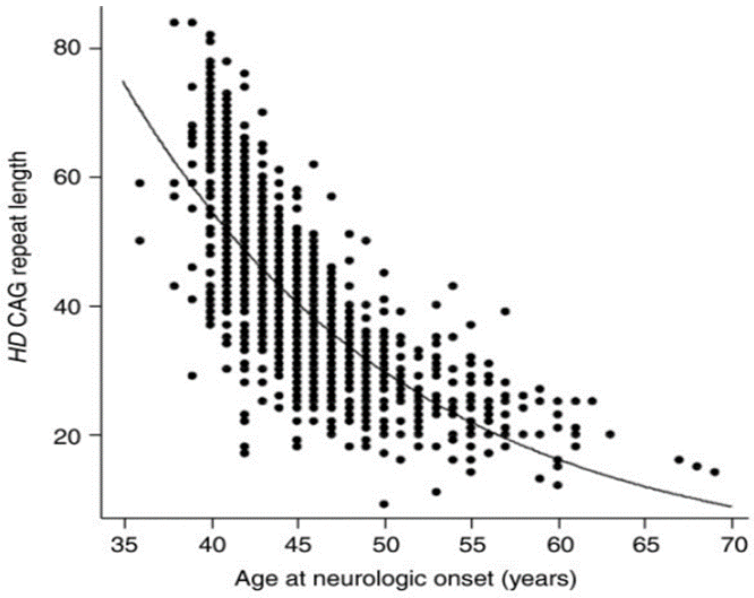


Figure 3: Inverse correlation of age at neurologic onset and HD CAG repeat length
Inverse correlation of age at neurologic onset and HD CAG repeat length: Inverse correlation of age at neurologic onset and HD CAG repeat length. The plot shows data points from 1,200 HD subjects of known age at neurologic onset. The measured CAG repeat length in blood DNA (x-axis) is plotted against age at neurologic onset (y-axis) for each individual. The line represents the best-fit simple logarithmic regression to the data (Gusella and Macdonald, 2009).

Repeat lengths in the range of 27 to 35 (intermediate allele) are also primarily not associated with the development of HD. However, there is the possibility of expansion upon transmission, resulting in the phenomenon of genetic anticipation (Apolinário et al., 2017). Some reports refer to intermediate alleles as "mutable normal alleles" since they have shown repeat instability upon transmission to subsequent generations (Goldberg et al., 1995). Specifically, intermediate alleles may undergo germline CAG repeat expansion, where the number of CAG repeats expands into the disease-associated range (Semaka et al., 2006). Thus, children of intermediate allele carriers are at risk of inheriting an HD allele with either full or reduced penetrance (Semaka et al., 2006). In some cases, even supportive neuropathological evidence of HD can be found (Ha and Jankovic, 2011, Panegyres and Goh, 2011). An expansion during the transmission is more likely to occur with longer repeat lengths in this region and also tends to occur with male inheritance (Zühlke et al., 1993).

CAG repeats in the range of 36 to 39 refer to incomplete penetrance associated with variable disease manifestation or late manifestation in the fifth and sixth life decades (Chaganti et al., 2017). Due to the ageing process represents late manifest HD substantial proportion of new diagnoses and has some unique features (Chaganti et al., 2017).

Full penetrance relates to the CAG length of more than 40 repeats, although CAG length larger than 50 is typically associated with disease onset between the ages of 20 and 30 (Nopoulos, 2016). Juvenile Huntington Disease (JHD) refers to the presence of a CAG length of more than 60 and occurs prior to the age of 21, which comprises about 5% of all HD cases (Quarrell et al., 2013). Within JHD, the CAG lengths over 60 are associated with an age of onset between 10 and 20 years, and the highest CAG numbers over 80 may manifest in childhood and diagnose prior to the age of 10 (Fusilli et al., 2018). For an overview, see Figure 4. The earliest reported diagnosis was in an 18-month-old child with a repeat length of over 200 CAGs (Nicolas et al., 2011).

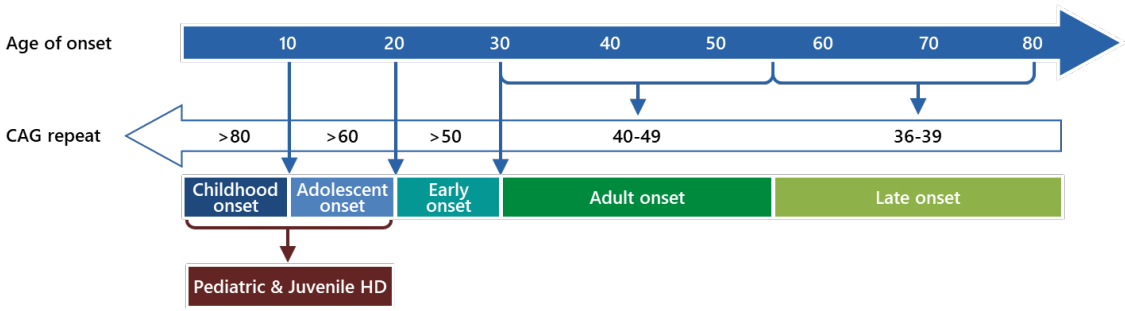


Figure 4: The relationship between CAG length and age of onset
This figure displays an approximations age of onset based on repeat length (Nopoulos, 2016).

3.3. Genetic Modifiers

Although the primary determinants of whether and when an individual will present with HD are the presence and length of the extended CAG tract, Gusella et al. showed that the disease manifestations and timing are influenced by other factors called genetic modifiers (Gusella and Macdonald, 2009). These genetic factors, independent of CAG repeat length, have also been shown to modify HD (Gusella and Macdonald, 2009, Holmans et al., 2017). The largest genome-wide association study (GWAS) in HD identified several genes involved in DNA repair that can modify the age of onset of the disease (Genetic Modifiers of Huntington's Disease Consortium, 2015). The finding confirmed the FAN1 (Fanconi anaemia FANC1/FANCD2-associated endonuclease) gene on chromosome 15 (Jones and Huang, 2012) and MTMR10 (myotubularin related protein 10) gene as HD genetic modifiers (Cannavo et al., 2007). Moreover, other significant associations were identified with RRM2B (a subunit of DNA damage p53-inducible ribonucleotide reductase M2B) and URB5 (a HECT domain E3 ubiquitin-protein ligase) on chromosome 8 (Genetic Modifiers of Huntington's Disease Consortium, 2015). In addition, the genetic pathway analysis in terms of the implicated gene pathways involved in DNA repair, mitochondrial fission and oxidoreductase activity were further examined and revealed an association between HD progression and a genetic variant in MSH3, associated with CAG somatic instability and highlighted the somatic expansion as a potential pathogenic modulator, informing therapeutic development in HD (Moss et al., 2017). It is known that the expanded CAG repeat tract is somatically unstable, undergoing progressive length increases over time (Telenius et al., 1994, De Rooij et al., 1995). Somatic instability is tissue-specific, with high levels found in the striatum and cortex (Kennedy et al., 2003) and occurs in post-mitotic neurons; furthermore, somatically expanded HD CAG repeats are transcribed and translated (Shelbourne et al., 2007). As the CAG repeat somatically expands in tissues, it is crucial for future genetic modifying approaches.

4. Neurobiology of Huntington Disease

4.1. Huntingtin Protein

4.1.1. Structure and Interactions

The *HTT* gene is responsible for coding a protein called huntingtin (HTT), a large (348 kDa), ubiquitously expressed protein (Gusella and MacDonald, 1995), the evolution of which can be

traced back to different species over millions of years (Palidwor et al., 2009). The polyglutamine tract first appeared in the sea urchin, which predated an ancestral polyQ sequence in a nonchordate environment and increased in length throughout the evolution of vertebrates, for humans to have the longest track (Tartari et al., 2008). Studies focusing on the structure of the HTT protein and its interaction with other protein systems have begun shortly after identifying the *HTT* gene.

The HTT protein consists of the polyglutamine sequence at the NH_2-terminus and multiple sequences called HEAT (Huntingtin, Elongation factor 3, protein phosphatase 2A, TOR1 (target of rapamycin 1)) (Wanker, 2000). In 1995, Andrade et al. described HEAT domains as essential for forming protein-protein interactions (PPI) (Andrade and Bork, 1995). HEAT repeats form a helix structure that is tightly packed to form a superhelix hydrophobic core that resists dissociation after proteolytic cleavage (Li et al., 2018). The N-terminal region has been extensively studied, containing the expandable polyQ stretch (Wanker et al., 2019).

Recently, a high-resolution cryo-electron microscopy structure was obtained for soluble full-length physiological wild type HTT (wtHTT) in complex with its interaction partner huntingtin-associated protein 40 (HAP40) (Guo et al., 2018). The wtHTT is a folded, a-helical protein consisting of three major domains: two large domains containing multiple HEAT repeats (N-HEAT and C-HEAT) located at the N- and C terminus wtHTT and connected by a smaller bridge domain of tandem repeats (Guo et al., 2018). HAP40 is also largely α-helical protein binding to the HTT on three domains by hydrophobic and electrostatic interactions, and thou stabilising the overall conformation of HTT (Guo et al., 2018). The protein structure is displayed in 3D complex with HP40 in Figure 5

Numerous studies have identified more than 350 partners of wtHTT (Saudou and Humbert, 2016), and more interactions partners are awaiting; however, many of these interacting proteins are subject to further validation. Protein function is often modulated by PPIs, and therefore defining the partners of a protein helps understand its activity (Schaefer et al., 2012).

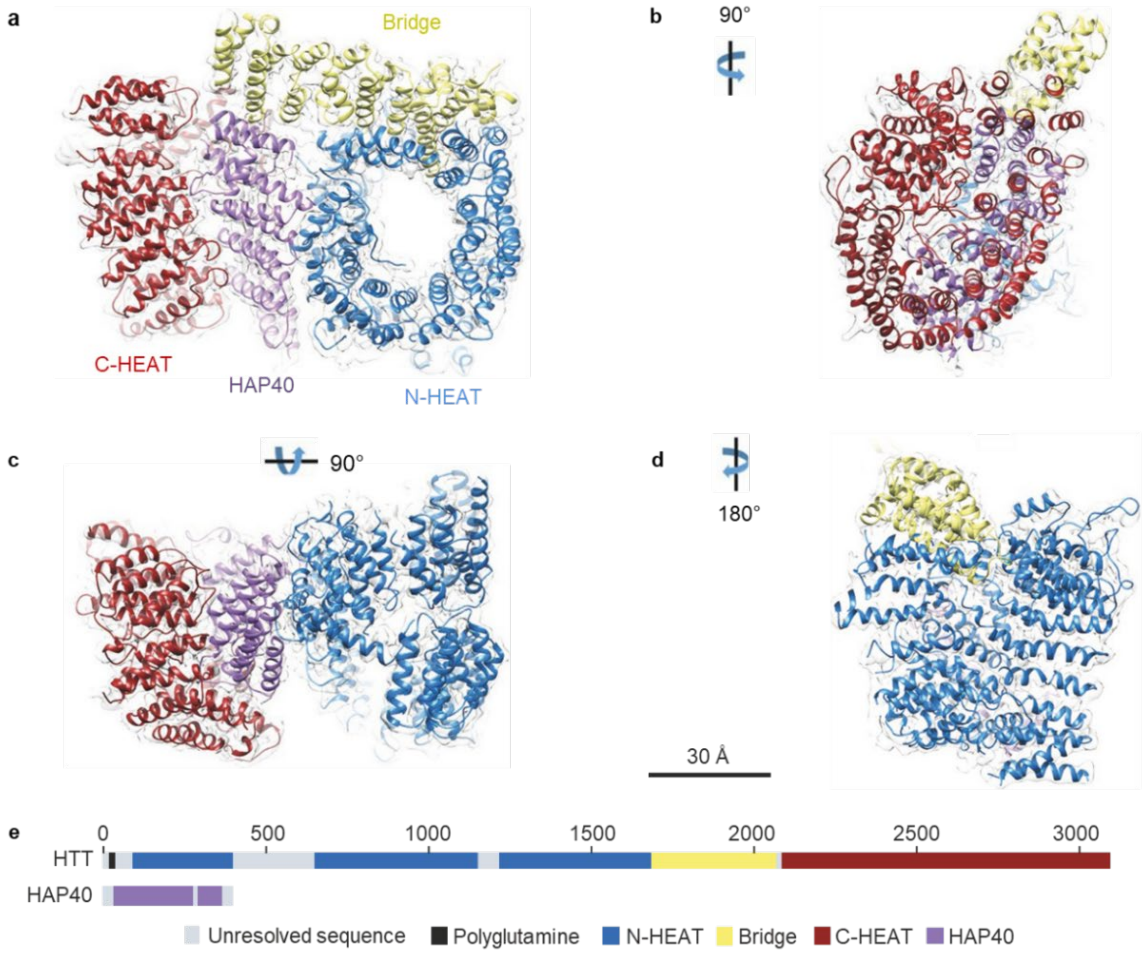


Figure 5: Architecture of the HTT–HAP40 complex
a–d, the reconstructed density map showing the atomic model in ribbon representation, with domains colour-coded as follows: HTT N-HEAT domain, blue; HTT bridge domain, yellow; HTT C-HEAT domain, maroon; HAP40, purple. a–d show different views of the complex as indicated. e, schematic of the domain organisation of HTT and HAP40 (Guo et al., 2018).

4.1.2. Functions

The Huntingtin protein (HTT) is essential for embryonic development: its complete inactivation in huntingtin-knockout mice causes embryonic death before the nervous system formation (Nasir et al., 1995). The wtHTT becomes vital for neurogenesis and participates in forming the central nervous system (CNS) for neural tube formation and neuroblast migration. Therefore, significantly reduced huntingtin levels are insufficient to support normal development (White et al., 1997).

The wtHTT is also linked to brain-derived neurotrophic factor (BDNF), which is particularly important for the survival of striatal neurons and corticostriatal synapses, as it also controls glutamate release and transmission (Jovanovic et al., 2000). The first study in 2000 by Metzler et al. identified the critical role of wtHTT in hemopoiesis, suggesting that wtHTT expression is required for the generation and expansion of hematopoietic cells (Metzler et al., 2000). There is also

evidence that the wtHTT presents neuroprotective effects in brain cells exposed to various apoptotic stimuli, such as serum deprivation, mitochondrial toxins, or the death gene transfection (Cattaneo et al., 2005). The wtHTT is involved in energy metabolism. Its deficits lead to interrupted interaction on the mitochondrial membranes, disrupting calcium homeostasis upon exposure to metabolic stress and thus leading to indirect excitotoxicity (Roze et al., 2008).

The wtHTT is a crucial protein in diverse cellular activities. It is involved in multiple cellular pathways: cellular dynamics (cytoskeleton, endocytosis, trafficking, and adhesion), metabolism, protein turnover, gene expression (transcription and RNA processing), and signal transduction(Cattaneo et al., 2005). The recent review from Saudou &Humbert refers to the wtHTT as a molecular scaffold due to its large size and stability. In this way, wtHTT serves as a hub that binds multiple partners in complexes to coordinate cellular processes; however, the complexes are regulated by the partner proteins temporally and spatially available on the HTT platform (Saudou and Humbert, 2016). The essential physiological feature is the ability of HTT to traffic between the nucleus and cytoplasm and as well functioning for a cargo of the vesicle and organelle along axons (Schulte and Littleton, 2011). Herby wtHTT regulates the assembly of dynein/dynactin complexes for various functions, and this dynein/dynactin scaffold is modulated by HTT phosphorylation (Caviston and Holzbaur, 2009). HTT is subjected to multiple posttranslational modifications that include phosphorylation, acetylation, palmitoylation, ubiquitylation and sumoylation and plays a role in future potential therapeutic targets to modulate the toxicity of mutant HTT (Caterino et al., 2018).

4.2. Cellular and Molecular Pathophysiology

The genetic cause of HD has been known since 1993; however, the molecular pathogenetic mechanisms that lead to the selective neurodegeneration typical of HD, especially in the striatum, are still not fully understood. There is strong evidence that the expression of the mutant HTT (mHTT) and its fragmentation is the underlying pathological mechanism of HD (DiFiglia et al., 1997). Fragments can be detected in transgenic HD mice models as well as in all brain regions of a young presymptomatic mouse model prior to detection of aggregates (Davies et al., 1997, Landles et al., 2010), and have also been isolated from human post-mortem HD brains (Landwehrmeyer et al., 1995). Fragments forming inclusion bodies have been reported from multiple brain regions, including the striatum, cerebral cortex, thalamus, cerebellum, brain stem, and spinal cord (DiFiglia et al., 1997). The highest expression occurs predominantly in neurons in the striatum, followed by globus pallidus, although a low but significant level of expression is seen in glial cells

(Landwehrmeyer et al., 1995). Although the mHTT transcripts fragments and protein are found at different levels through most human tissues, numerous studies have shown fragments in the heart, placenta, lung, liver, muscle, kidney, pancreas and testes (Li et al., 1993, Mielcarek, 2015, Pinto et al., 2020, Selvaraj et al., 2020). However, it is also known that mHTT expression is higher in the nervous system than in other tissues (Reiner et al., 2011). The smallest huntingtin fragment is generated through an aberrant splicing process that leads to the production of a pathogenic HTT exon1 protein (Sathasivam et al., 2013). Other fragments are produced through cleavage by caspases, calpains and other proteases processes (Marques Sousa and Humbert, 2013).

Overall, the mHTT protein has many effects in cells, including abnormalities in cellular proteostasis mechanisms (Bence et al., 2001). It enters the nucleus and alters gene transcription (Seredenina and Luthi-Carter, 2012). Numerous additional cellular mechanisms of the HD pathogenesis have been discussed, including the toxicity of mHTT or amino-terminal fragments of mHTT with aggregation of poly-glutamine-expanded mHTT fragments in the cytoplasm and nucleus as well as a partial loss of physiological functions of the HTT as a consequence of the mutation (Arrasate and Finkbeiner, 2012). The mHTT is subjected to multiple posttranslational modifications, including phosphorylation, acetylation, palmitoylation, ubiquitinylation and sumoylation (Marques Sousa and Humbert, 2013).

Further, the removal of damaged organelles and aggregated protein fragments by delivering them to the lysosomes for degradation is critical in the process called autophagy. Autophagy defects have been consistently observed in HD (Steffan, 2010). Particularly, a high amount of autophagosome formation with reduced capacity to degrade aggregated proteins and organelles has been described in HD models (Martin et al., 2015). Further, the mHTT interrupt post-Golgi trafficking to lysosomal compartments for autophagy by delocalizing the optineurin/Rab8 complex, which, in turn, affects the lysosomal function (Toro et al., 2009). Autophagosomes in neurons under basal conditions are generated at distal axons. They are retrogradely trafficked to the cell body so that the mHTT presence may block the retrograde transport of autophagosomes along the axon leading to defective cargo degradation (Wong and Holzbaur, 2014). In summary, the inefficient clearance of mHTT fragments leads to further pathology and neurotoxicity in HD. On the other hand, it may be assumed that wtHTT may regulate its clearance. Moreover, mHTT may increase the expression levels of autophagy genes in the striatum, particularly in the caudate nucleus, mRNA expression of light chain 3A (LC3A), Unc-51-like kinase 2 (ULK2), and lysosome-associated membrane protein 2 (LAMP2) is significantly increased, whereas; PTEN-induced kinase 1 (PINK1) and FK506 binding protein 1A are significantly decreased (Martinez-Vicente et al., 2010). Additionally, increased expression of LC3A and ULK2 lead to early autophagy induction and

autophagosome formation in HD (Martinez-Vicente et al., 2010). A decrease in PINK1 expression induces mitochondrial fragmentation and mitophagy (Kamat et al., 2016). HD is associated with increased mitochondrial fragmentation and resulting mitochondrial pathology (Kumar and Ratan, 2016).

The mHTT and its cleavage products lead to damage and loss of striatal projection neurons, medium spiny neurons (MSNs), cortical projection neurons and other cells of the CNS due to molecular mechanisms that are not yet understood in detail (Reiner et al., 2011, Waldvogel et al., 2015). Further studies in model organisms and HD patients have identified numerous pathophysiological mechanisms that play an essential role in the complex pathogenesis of HD. These include transcriptional changes, alterations in glutamatergic transmission with N-methyl-D-aspartate (NMDA) receptor dysregulation (Perry et al., 1973, Suhr et al., 2001), disturbances in Ca2+-dependent signal transduction (Kolobkova et al., 2017), disruption of K+ homeostasis (Zhang et al., 2018), and deficits in cellular energy metabolism due to alterations in mitochondrial function (Mochel and Haller, 2011). All these disease mechanisms are functionally interconnected and influence each other.

5. Neuropathology of Huntington Disease

5.1. Basal Ganglia Anatomy

The primary pathology site in HD is the basal ganglia (BG). In the past decade, substantial advances have been made in our understanding of BG anatomy in experimental models and post-mortem studies of the anatomic changes associated with human diseases of the BG (Albin et al., 1989). BG are a group of interconnected subcortical nuclei. According to anatomical nomenclature, the corpus striatum (caudate nucleus and putamen), the globus pallidus (globus pallidus externum et internum), the amygdala and the claustrum (Splittgerber and Snell, 2019). The pallidum and the putamen together are called the lentiform nucleus. The subthalamic nucleus (corpus Luysi) and substantia nigra (especially the pars reticulata morphologically and chemically similar to the globus pallidus internus) refer to the BG, given their anatomical and functional involvement (Parent, 1986). Thus, together with the striatum and the pallidum, they form the "dorsal compartment" of the basal ganglia, responsible for motor and associative functions. The "ventral compartment" of the basal ganglia include the nucleus accumbens septi (ventral striatum) and the upper part of the substantia innominata (ventral pallidum) (Schröder et al., 1975, Parent, 1986). These portions were assigned to

the BG later as it became apparent that they shared many structural similarities. The ventral compartment is associated with limbic functions. A very close connection to the basal ganglia, in terms of connectivity and neurotransmitter characterisations shared by nucleus basalis Meynerti (cholinergic nucleus), substantia nigra, pars compacta (dopaminergic nucleus A9) and area ventralis tegmenti Tsai (dopaminergic section A 10) (Nakano et al., 2000). An overview of the BG anatomy is in Figure 6.

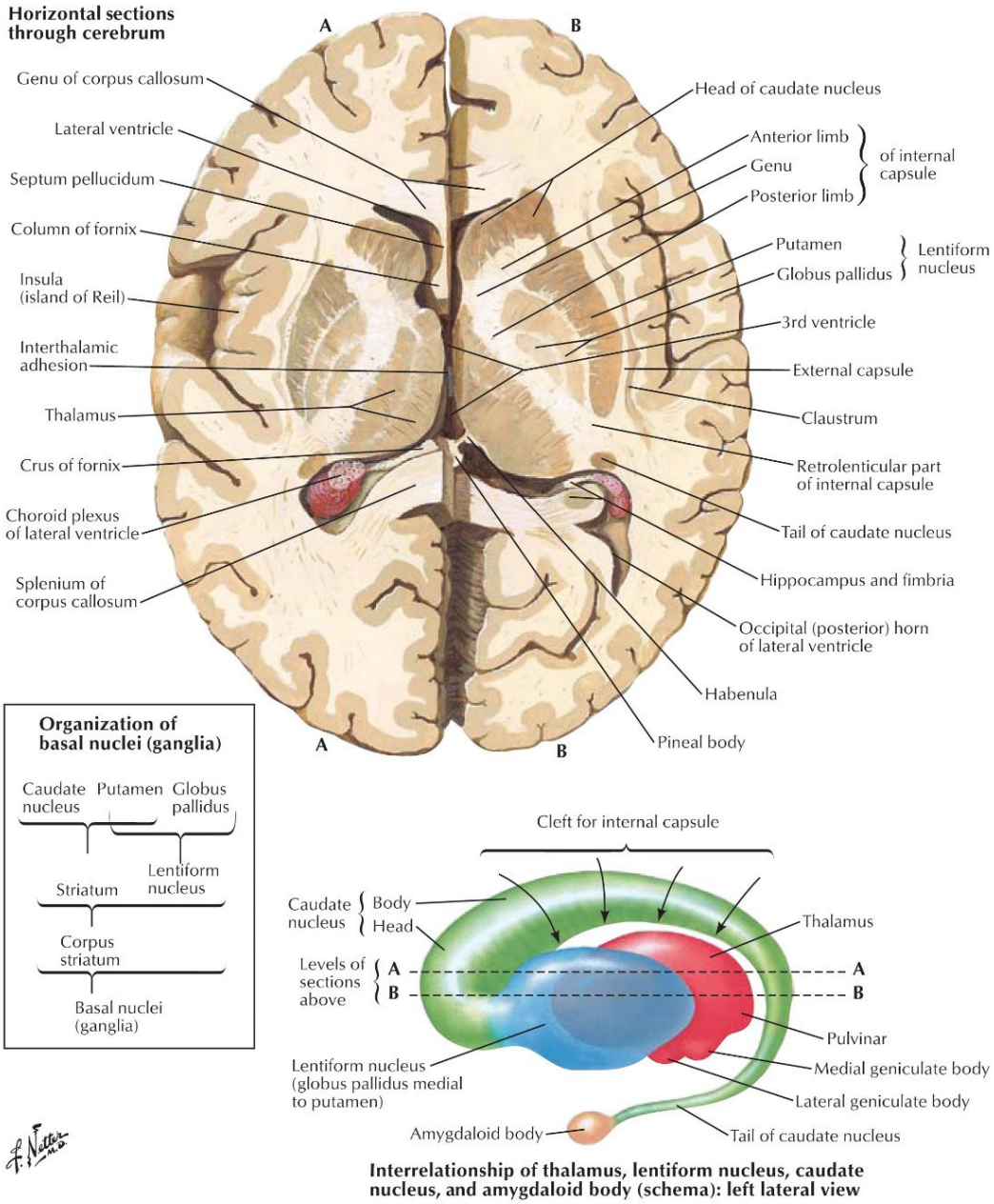


Figure 6: Basal ganglia anatomy
The anatomical organisation of the basal ganglia: A and B section shows a nucleus caudatus in the full size and its relationship to the thalamus and nucleus lentiform—picture licensed from the Netter Images, Elsevier, 18.09.2021.

5.2. Cell Populations in Basal Ganglia

The striatum consists of two major neuron types, projection neurons and interneurons, while globus pallidus consist mainly of projection neurons (Kreitzer and Malenka, 2008). The striatal projection neurons, also called the Medium Spiny Neurons (MSNs), forming about 95 % of the striatal neuron population (Graveland and Difiglia, 1985), are transmissions the excitatory inputs in the dorsal and ventral striatum and are uniformly mediated by glutamate receptors, with AMPA and kainate subtypes predominating transmission (Nakano et al., 2000). Functionally, MSNs have two distinct receptor types, Dopamine (DA)-type 1 and DA type 2. Approximately 40% of striatal MSNs express both DA1-type and DA2-type receptors (Märtin et al., 2019). The interneurons of the striatum have been shown to make up around 5% of the total neuronal population (Graveland and Difiglia, 1985). Large cholinergic interneurons release acetylcholine, which has a variety of essential effects in the striatum and are themselves influenced by dopamine via DA-type 5 receptors (Bergson et al., 1995, Gonzales and Smith, 2015). Different types of GABAergic interneurons are present in the striatum. The best known are parvalbumin-expressing interneurons (fast-spiking interneurons) and GABAergic interneurons expressing tyrosine hydroxylase, somatostatin, nitric oxide synthase and neuropeptide-Y (Tepper et al., 2010, Ibanez-Sandoval et al., 2011). The highly selective and specific synaptic connections between different interneuron subtypes and MSNs and between different GABAergic interneurons themselves provide a base for the hierarchical control of further striatal interneurons (Tepper et al., 2018).

As the striatum is not a homogeneous structure, the topographical organisation of the striatum comprises two main compartments called striosomes (also known as patches) and matrix (Brimblecombe and Cragg, 2017). Striosomes form a three-dimensional, labyrinth-like structure connected to the matrix. Striosomes maintain histochemically high levels of the μ-opioid receptor (MOR), substance P, DA-type 1 receptor, metenkephalin, calretinin, pro-dynorphin, GAD-2 and EGR-1 expression. The matrix, by contrast, is enriched with calbindin, somatostatin, enkephalin, DA-type 2 receptor, and cholinergic markers, including acetylcholine esterase (AChE) and choline acetyltransferase (ChAT) (Brimblecombe and Cragg, 2017). The globus pallidus internus and substantia nigra pars reticularis are morphologically and biochemically similar. The vast majority of cells are large and multipolar projection neurons. There are relatively few interneurons in the pallidum and substantia nigra pars reticularis. The most important neurotransmitter is the inhibitory GABA (Nakano et al., 2000).

5.3. Neuropathology of Huntington Disease

The basal ganglia are most affected by the pathological process in HD, especially the striatum (Vonsattel et al., 1985). The caudate, which is prominent in the lateral ventricle, may be reduced to a thin strip of tissue, leading to a typical enlargement of the anterior horns of the lateral ventricles (Vonsattel et al., 1985). Thalamus and globus pallidus are also subsequently affected (Lange et al., 1976). Further, the white matter involvement is well documented and approximately around 20% reduction in brain weight (Vonsattel et al., 1985, Mann et al., 1993).

In early 1990, Vonsattel et al. revealed the classification system for HD pathology based on the neuropathological changes in the Caudate-Accumbens-Putamen region to the four grades in ascending order with consideration of the clinical features as displayed in Table 2 (Vonsattel et al., 1985):

	Neuropathological Abnormalities
Grade 0	Clinical evidence for HD but no abnormalities be related to HD detected on macro and microscopic level
Grade 1	No macroscopic abnormalities in the caudate or putamen but moderate fibrillary astrocytosis at the microscopic level 8
Grade 2	Macroscopic changes in the caudate and putamen but no macroscopic changes in the globus pallidus,
Grade 3	The lateral segment of the globus pallidus with fibrillary astrocytosis and the medial segment of the globus pallidus no changes,8
Grade 4	Shrunken caudate, widened anterior horn of lateral ventricle and smaller nucleus accumbens

Table 2: Classification system for HD pathology
Neuropathological abnormalities described by Vonsatellel et al. are organised in the four ascending grades considering the clinical features (Vonsattel et al., 1985).

Neuropathological abnormalities also occur in grades 3 and 4 in other brain regions, including the thalamus, subthalamic nucleus, white matter, and cerebellum. The cortex atrophy is present even in stages 3and 4 in the different variability (Vonsattel et al., 1985). It needs to be highlighted that the recent studies in magnetic resonance imaging (MRI) have confirmed these early pathological findings confirm the loss of caudate and putamen grey matter volume and loss of both striatal and cortical white matter in very early stages of HD (Tabrizi et al., 2011, Paulsen et al., 2014b, Mason et al., 2018).

However, in 2012 this classification was re-evaluated to explore the relationship between striatal involvement in HD and involvement in other brain regions, CAG repeat size, onset age, and other

factors (Hadzi et al., 2012). According to the main pathology site, the two brain clusters (striatum and cortex) have been identified in relation to the CAG repeat length size, age at HD onset, and brain weight, suggesting that neuropathologic involvement does not proceed in a strictly coupled fashion. The pattern and extent of involvement vary substantially from one brain to the next, suggesting that regional involvement in the HD brain is modified by factors that, if identified, may lend insight into novel routes to therapeutics (Hadzi et al., 2012).

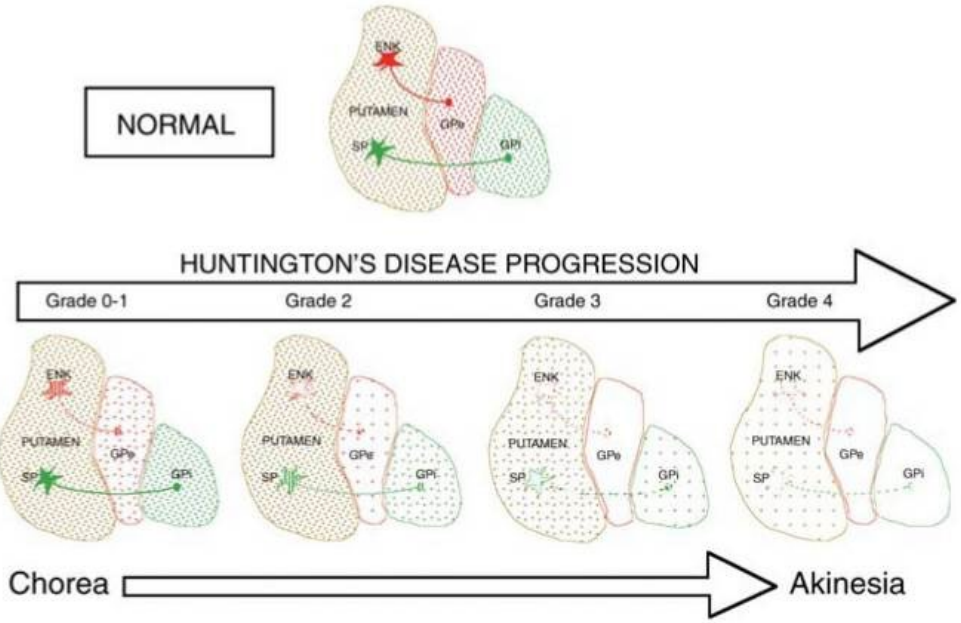


Figure 7: Basal ganglia pathology to HD progression
Illustration of the neuron loss in basal ganglia during the progression of HD and the relation to the development of motor symptoms. GPe – Globus Pallidum externum, GPi - Globus Pallidum internum, Enk – Enkephaline,

The following section details how HD affects these various neuronal populations. Notably, striatal neuron loss in HD largely involves projection neurons, with most striatal interneuron types highly resistant to HD (Graveland and Difiglia, 1985). An overall reduction in glia also occurs, but the ratio of glia to neurons increases due to the extensive neuronal loss (Jansen et al., 2017). Thus, reactive microglia are already present at the beginning of the pathological process in the pallidum, neostriatum and cortex and the surrounding white matter. Its density increases with neuronal loss (Sapp et al., 2001). In degenerating neurons, numerous inclusions are present, but their functional significance remains unclear (DiFiglia et al., 1997).

Early post-mortem histochemical studies show normal or slightly elevated dopamine and glutamate levels in the striatum, whereas GABA and glutamate decarboxylase and choline acetyltransferase enzymes are significantly reduced (Bird and Iversen, 1974, Perry et al., 1985). Some striatal neuropeptides such as substance P, enkephalins, angiotensin-converting enzyme and

cholecystokinin are reduced (Martin 1986, Perry 1973, Spokes 1981, (Bird and Iversen, 1974, Perry et al., 1985).

As mentioned above, the post-mortem studies revealed that although mutant HTT is ubiquitously expressed, the most prominent pathology also occurs in the cerebral cortex, besides the striatum (Graveland and Difiglia, 1985, de la Monte et al., 1988). Cortical pyramidal neurons (CPNs) send extensive projections to the striatum, forming the corticostriatal pathway that, among other functions, shapes motor behaviour (Vonsattel et al., 1985). As the development of involuntary movements is a prominent feature of the HD phenotype, dysfunctional cortical input to the striatum is likely to constitute a key component of HD neuropathology (Rosas et al., 2006). The cortical atrophy and loss of CPNs is a neuropathological hallmark of HD. However, most of these studies were performed on tissue from neuropathological grades 2–4 (more details in Table 2); less about the cortical atrophy in early and premanifest HD stages (Hadzi et al., 2012). There is a reduction of about 30% in numbers of CPNs in cortical layers III, V and VI (Cudkowicz and Kowall, 1990).

The primary motor cortex (Brodmann's area 4) and the premotor area (Brodmann's area 6) in HD brains present a significant reduction in the CPNs and layer disorganization (Macdonald and Halliday, 2002). The extent of cortical atrophy in motor areas correlates with the extent of the HD motor phenotype, also suggesting that in HD patients for whom mood alterations are the primary symptom, the loss of CPNs is most prominent in the cingulate cortex processes emotion (Thu et al., 2010). Besides the cortical pathology, there is also a significant decrease of about 40% in neuronal number and shrinkage of pigmented and non-pigmented neurons in the substantia nigra, referring to the substantia nigra as a site of a primary degeneration in HD (Oyanagi et al., 1989).

Moreover, there is no relationship between the number of dopaminergic neurons and the development of the motor phenotype in terms of chorea and dystonia in HD (Albin et al., 1989). In the early investigation of Jeste et al., a highly significant reduction in Purkinje cell density in the cerebellum was detected, suggesting that the neuronal loss in HD may not be restricted to small and medium-size neurons (Jeste et al., 1984). These changes occurred predominantly in juvenile forms of HD (Rodda, 1981, Rüb et al., 2013).

6. Pathophysiology of Basal Ganglia in Relationship to Huntington Disease

Basal ganglia function is mainly associated with processing cortical motor impulses to the brainstem's frontal cortex and motor centres (Parent et al., 1995). Thus, in conjunction with the frontal lobes, the basal ganglia are involved in selecting, planning, and initiating movements (Voorn et al., 2004). However, the basal ganglia also play a significant role in regulating emotions and cognitive functions (Cummings, 1993).

6.1. Basal Ganglia Circuits

The basal ganglia system assures a flow of information that originates in the entire cerebral cortex and projects back to the sole frontal cortex by passing this information through the circuit loops and adjusting in the striatum, the globus pallidus and the subthalamic nucleus (Albin et al., 1989). Information sent back to the frontal cortex is not a replication of cortical commands but a piece of completely new information processed in specific networks of striatal, pallidal and subthalamic neurons (Yelnik, 2008). These neuronal networks are regulated and consolidated by dopaminergic and cholinergic reinforcement learning, becoming available for automatic execution on cortical request (Prensa et al., 2000).

Albin presented the basic circuit model of the basal ganglia functions that involve "direct" and "indirect" pathways (Albin et al., 1989). It has represented the key knowledge on basal ganglia function for almost three decades. The main BG circuits are named after their function or origin in the cortex. As part of the auxiliary motor systems, the basal ganglia have an inhibitory effect on cortical and subcortical motor functions (Alexander, 1986). The striatum receives information from various cortical areas. It transmits it to the pallidum or substantia nigra pars reticularis and from there to the thalamic nuclei and thence to the frontal cortex (Alexander, 1986). The pallidum and substantia nigra pars reticularis are linked to the motor stem structures. Connections leading from the pallidum to the reticular formation modify the trunk and limb movements. The substantia nigra pars reticularis is connected to the tectum and affects the neck, head, and eyeball movements.

Further, a circuity model proposed by Delong postulates that the cortical projection from the frontal cortex comprises five different circuits, oculomotor, motor, dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate, which cross through the basal ganglia direct and indirect pathways (striatum, pallidum and substantia nigra) as separate channels, which remain segregated

up to their projection back to the frontal cortical areas from which they arise (Delong and Wichmann, 2007). Although the BG circuit continues to evolve and more information is available, the traditional classification is used in this thesis. It allows the presentation of motor, behavioural and cognitive changes specific to each circuit and the relevance of the frontal-subcortical circuits to various neuropsychiatric disorders (Rosas et al., 2008). The five frontal-subcortical circuits primarily involved in motor, behavioural and cognitive changes will be highlighted. The motor circuit, originating in the supplementary motor area, and the oculomotor circuit, originating in the frontal eye fields, are involved in motor functions (Groenewegen, 2003). The dorsolateral prefrontal, orbital frontal and anterior cingulate circuits are responsible for executive functions, social behaviour and motivational states in humans (Cummings, 1993).

6.1.1. Motor Circuit

The motor circuit originates from neurons in the primary sensory, premotor, primary and supplementary motor cortex. These areas project topographically to the putamen, which in turn projects to specific parts of the globus pallidus external, internal, and substantia nigra pars reticularis, where it connects to the ventrolateral, ventral anterior, and centromedial nuclei of the thalamus, which project back to the motor cortex. The motor circuit serves to process information for limb and trunk movement (Mega and Cummings, 1994).

6.1.2. Oculomotor Circuit

The oculomotor circuit originates in the frontal visual cortex (Brodmann's area 8) and posterior parietal cortex. The fibres then project to the corpus nuclei caudatus and continue to the globus pallidus internus and substantia nigra pars reticularis. They reach the mediodorsal thalamic nuclei and close the loop by projecting back to the frontal visual field. The oculomotor circuit mediates oculomotor movements in response to visual stimuli (Alexander, 1986).

6.1.3. First Associative Circuit

The first associative, also called the first cognitive or the dorsolateral prefrontal circuit, originates in Brodmann's areas 9, and 10 on the lateral surface of the anterior frontal lobe and projects to the head of the caudate nucleus then continue to the globus pallidus internus, and substantia nigra pars reticulata. The mediodorsal thalamus sends fibres back to the circuit origin in the dorsolateral frontal cortex. The association circuit modulates spatial memory and evaluates one's behaviour (Graybiel, 1995).

6.1.4. Second Associative Circuit

The second cognitive/associative pathway, also called the lateral orbitofrontal circuit, originates in the orbitofrontal cortex, temporal gyrus and anterior cingulate cortex and sends fibres to the ventromedial caudate nucleus, followed by a projection into the globus pallidus internus and substantia nigra pars reticulata before looping into the cortex via the ventromedial thalamus (Graybiel, 1995).

6.1.5. Limbic Circuit

The anterior cingulate circuit, also called the limbic circuit, originates in the anterior cingulate cortex (Broadmann's area 24). The neurons project to the ventral striatum, including the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle. Projections from the ventral striatum connect to the globus pallidus internus, ventral pallidum and rostrodorsal substantia nigra, and pass to the anteroventral thalamus. The anterior cingulate circuit is closed with projections from the ventral anterior thalamus back to the anterior cingulate cortex. Limbic system connections involve both the anterior cingulate and medial frontal regions. The limbic circuit regulates visceromotor and somatomotor centres of the trunk and spinal cord (Mega et al., 1997).

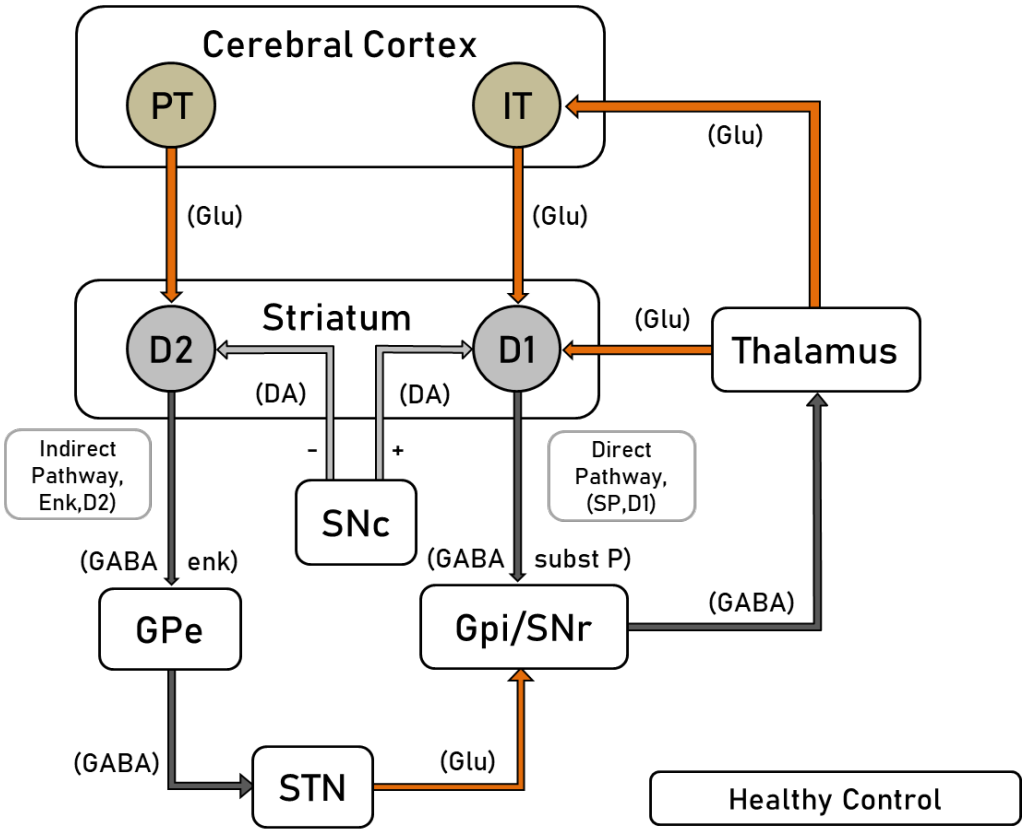


Figure 8: Simplified schematic representation of basal ganglia circuitry
The figure highlights cortical and striatal outputs as originally proposed by Albin et al. 1989.: Red arrows represent excitation, black arrows represent inhibition. Corticopyramidal Neurons (CPNs) of intratelencephalically projection (IT) project to the striatonigral D1-enriched Medium Spiny Neurons (MSNs) of the direct pathway. Pyramidal tract (PT)-type CPNs of the pyramidal tract (PT)-projection to the striatopallidal D2-enriched MSNs of the indirect pathway. Neurotransmitters are indicated in parenthesis. DA, dopamine; enk, enkephalin GABA, gamma-Aminobutyric acid; Glu, glutamate; subst P, substance P; Abbreviations: Gpi, Globus pallidus internus; Gpe, Globus pallidus externus, STN, Subthalamic Nucleus, substantia nigra pars compacta (SNc); substantia nigra pars reticulata (SNr).

6.2. Pathophysiology of the Huntington Disease

6.2.1. Basal Ganglia and Motor Manifestations

The motor symptoms in patients with manifest HD, including chorea and dystonia, reflect dysfunction of the BG or their circuits (Mega et al., 1997, Reiner et al., 2011). As the basal ganglia are a highly interconnected group of subcortical nuclei, atrophy in one or more of them can significantly impact other brain regions (Rubinsztein et al., 1996). For this reason, the atrophy of the striatum is a key element in the pathological process, as it receives projections from the entire cortex and then affects the other regions in which the projections radiate, the globus pallidus and the substantia nigra pars reticularis (Vonsattel et al., 1985). The afferent fibres from the primary and secondary motor, premotor, and cortical sensory areas pass to the striatum and connect via excitatory glutamate synapses to GABAergic mMSNs (Parent et al., 1995). Underlying pathological

changes with initial loss of MSNs on the indirect pathways of the striatum, resulting in the loss of the direct pathways and cell death, explain the typical pattern of movement disorders in HD (Plotkin and Surmeier, 2015).

Histopathological studies showed that these MSNs, which represent about 95 % of all striatal neurons, are selectively affected in the early stages of the disease (André et al., 2010). These findings are supported by MRI, which initially shows atrophy in the striatum and white matter tracts connecting the striatum to the cortex, followed by the spread of atrophy throughout the entire cortex (Rosas et al., 2008). The striatal efferent fibres lead to the globus pallidus internus et externus and the substantia nigra (Parent et al., 1995). The fibres from the nucleus caudatus terminate mainly in the dorsal half of the globus pallidus and fibres from the putamen in its caudal half (Vonsattel et al., 1985). In this way, the GABAergic MSNs form the direct motor pathway and project axons directly to the globus pallidus internus and substantia nigra pars reticularis (Alexander, 1986, Albin et al., 1989). These neurons have D1 receptors and modulatory peptides substance P and dynorphin and have a direct inhibitory effect on the globus pallidus internus and substantia nigra pars reticularis (Nakano et al., 2000).

The indirect motor pathway connects the striatum to the globus pallidus internus and substantia nigra pars reticularis via the globus pallidus externus and the nucleus subthalamic. Here, DA-type 2 receptors and the peptide enkephalin are expressed (Prensa et al., 2000). Connections from the striatum to the globus pallidus externus follow the nucleus subthalamic, containing glutamate to activate the globus pallidus internus and substantia nigra pars reticulata. Stimulating neurons of the indirect motor pathway causes inhibition of the globus pallidus externus, leading to disinhibition of the nucleus subthalamic excites the globus pallidus internus and the substantia nigra pars reticularis (André et al., 2010). The coexistence of direct and indirect motor pathways modulates stem and thalamocortical structures involved in motor programs. More details are displayed in Figure 8: Simplified schematic representation of basal ganglia circuitry. In early HD, post-mortem studies have shown that MSN of the indirect pathway is particularly vulnerable (Reiner et al., 2011), as shown in Figure 9. The function of glutamate and dopamine and other important neurotransmitters in basal ganglia function in the intact brain, and different HD stages are also displayed.

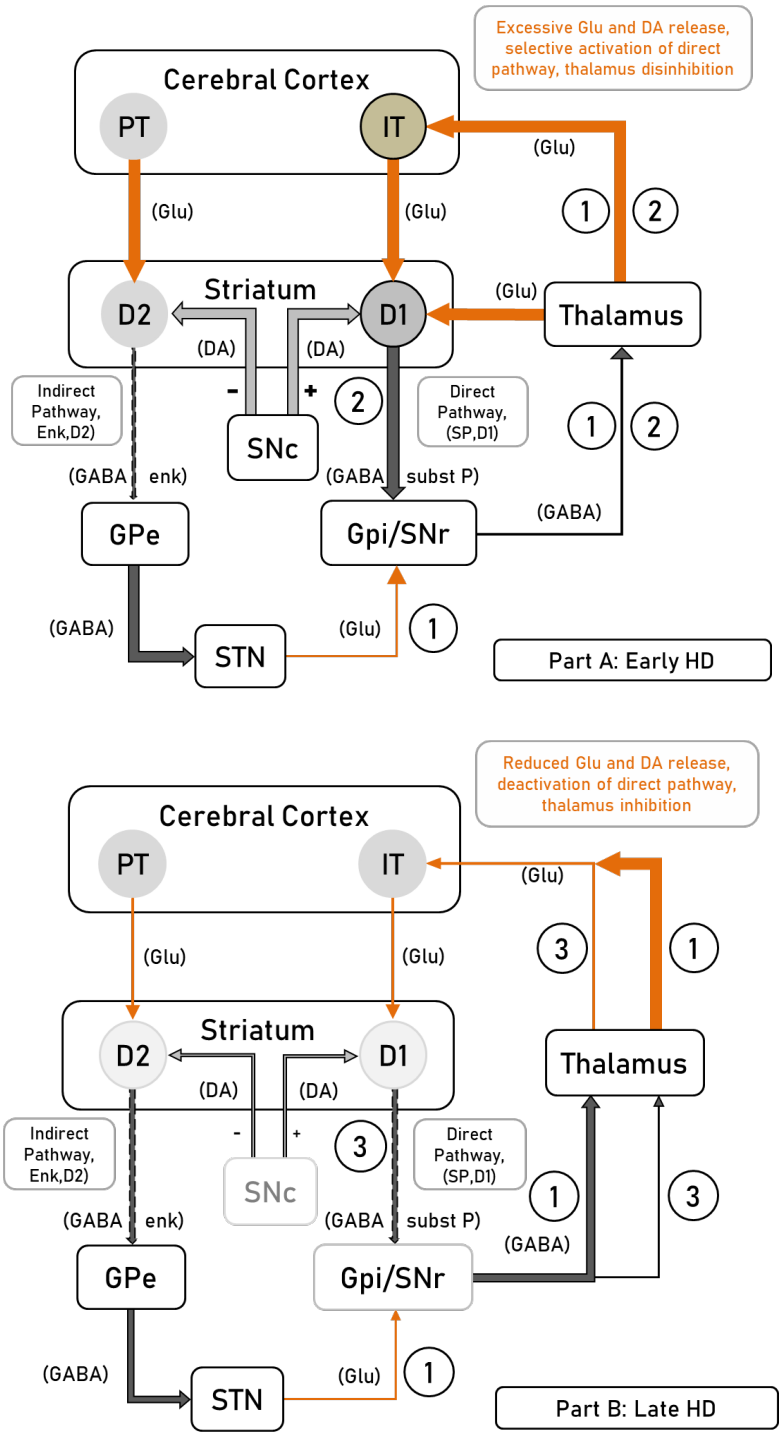


Figure 9: Simplified schematic representation of basal ganglia circuitry in early and late HD
Part A: *In **early HD**, cortical dysfunction induces increased glutamate release and dopamine levels in the striatum that trigger selective dysfunction of D2-receptor MSN (indirect pathway) and overactivation of D1-receptor MSN. An imbalance between the direct and indirect pathways could induce motor deficits, such as hyperkinesia, by two pathways: Imbalance between the direct and indirect pathways induces hyperkinesia via two pathways: **(1)** Selective dysfunction/degeneration (dashed lines) of enkephalin-containing MSNs leads to decreased release of GABA in the GPe and its disinhibition. In turn, overactivation of GABA neurons of the GPe leads to increased release of GABA and inhibition of STN, which decreases glutamate release and decreases the activity of the GPi and SNr **(2)**. Overactivation of the direct pathway MSNs (by abnormal DA modulation and/or excessive glutamate) leads to increased release of GABA and inhibition of GPi and SNrHence, alterations in both pathways induce inhibition of GPi and SNr GABA neurons and a decreased release of GABA in the thalamus. Disinhibition of the thalamus is responsible for increased glutamate input to the cortex that could potentially cause hyperkinesia. **Part B:** In **late HD,** corticostriatal and nigrostriatal inputs progressively degenerate, leading to decreased striatal Glu and DA release. Low striatal Glu and DA levels trigger dysfunction of both direct and indirect pathway MSNs. An imbalance between the direct and*

indirect pathways induces hyperkinesia and hypokinesia via two pathways: (1) Alterations in the indirect pathway are like early HD and lead to hyperkinetic movements (3). Dysfunction/degeneration of direct pathway MSNs induces the decreased release of GABA and disinhibition of GPi and SNr. Increased activity in GPi and SNr leads to inhibition of the thalamus and hypokinesia. Depending on the stage of dysfunction of direct and indirect pathway MSNs, activity in the basal ganglia could result in hypokinesia or hyperkinesia. It would explain why some symptomatic patients display both chorea and akinesia. Abbreviations: DA= dopamine, Enk = enkephalin; GABA= gamma-aminobutyric acid, Glu = glutamate; GPe = globus pallidus externus; GPi = globus pallidus internus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; STN = subthalamic nucleus, ; SP= substance P.

The deficits in the early stages of HD are dominated by impairment of the indirect motor pathway. Initially, GABAergic neurons using the neuromodulator enkephalin are more affected by degenerative processes. As a result of the reduction in GABA, there is not a sufficient inhibition of the globus pallidus externus, which increases its production of GABA and thus over inhibits the subthalamic nucleus, which reduces glutamate production and thus inhibits GABA production in the globus pallidus internus. The thalamus responds by overproducing glutamate, causing inadequate excitation of the motor cortex, leading to choreatic dyskinesia (Albin et al., 1989). In the late stages of HD, dysfunction of the direct motor pathways is clinically predominant. There is a massive loss of gabaergic neurons with substance P and dynorphin in the striatum. Due to the reduction in GABA levels, the globus pallidus internus is inadequately inhibited, leading to increased own GABA production. As a result, the thalamic inhibition activity is coupled with a reduction in glutamate production and, therefore, a lack of activation of the motor cortex, resulting in bradykinesia to akinesia. Bradykinesia occurs due to abnormal signalling from the basal ganglia to the supplementary motor area, involving initiation and performance of sequenced movements (Albin et al., 1989). It is also important to mention that a very common and early symptom in patients with HD is a slowing down of oculomotor movement, specially saccadic movements resulting from lesions in the paramedian pontine reticular formation, particularly the nucleus pontis centralis caudalis (Koeppen, 1989).

6.2.2. Basal Ganglia and Cognitive and Behavioural Manifestations

The striatum can be anatomically and functionally divided into ventral and dorsal regions; the larger dorsal striatum above the commissure anterior will be often referred to as motor striatum and is connected to the associative and sensor-motor cortical areas (Flaherty and Graybiel, 1996). The ventral striatum is often referred to as the accumbens nucleus, olfactory tuberculum and part of the putamen caudal to the commissure anterior and relates to the limbic system (Karcher et al., 2019). This anatomical-functional division interprets clinical symptoms (Cummings, 1993, Tekin and Cummings, 2002). Figure 10 shows the simplified organizations of the fronto-subcortical circuits. Numerous early studies showed that the ventral striatum is connected through the circuit loops to different frontal lobe areas and influences different mental functions (Cummings, 1993, Mega and

Cummings, 1994, Tekin and Cummings, 2002). Impairments mainly manifest in the dorsolateral circuit in executive functions: stimulus inhibition and preference, planning and task solving (Graybiel, 1997), the orbitofrontal circuit whose impairment is manifested mainly by personality changes: impaired interest, motivation, initiative, behavioural disinhibition, emotional lability, inadequate euphoria and irritability (Mega and Cummings, 1994). Moreover, the mediofrontal (anterior cingulate) circuit, whose impairment is manifested primarily by signs such as immobility, incontinence, apathy, abulia, loss of communication and non-acceptance of food (Flaherty, 2005).

BG dysfunction is always associated with neurotransmitter imbalance. The degree of impairment of individual circuits and the combination of symptoms gives rise to individual manifestations of the patient's psychological dysfunction. Dopamine signalling in the striatum is critical for various behaviours, including movement, behavioural flexibility, response to reward and many forms of learning. Therefore the alterations to dopamine transmission contribute to pathological features in HD (Koch and Raymond, 2019). The corticostriatal system also supports and controls the skilled, flexible behavioural actions that define a healthy life. Thus, the disturbances are causing behavioural

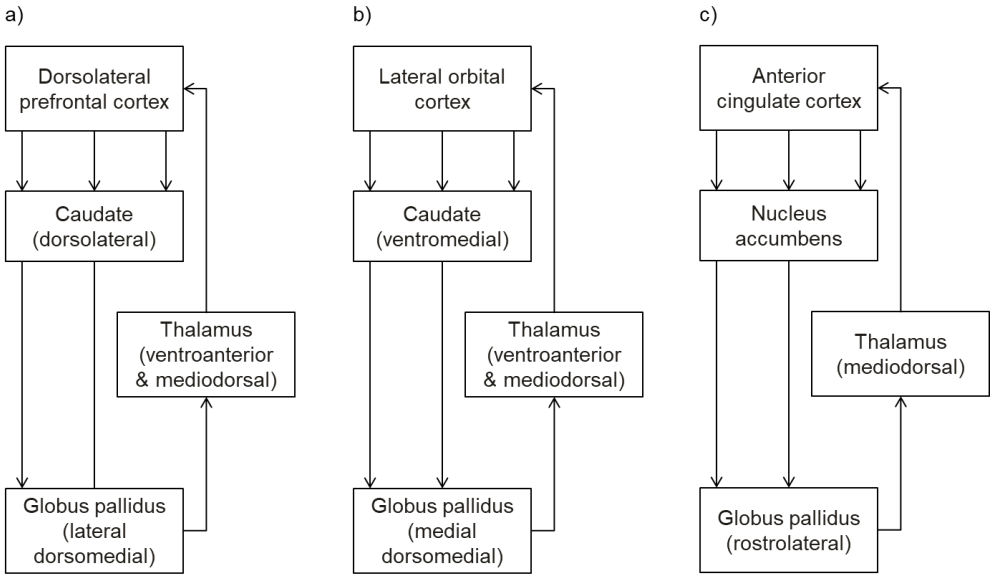


Figure 10: Simplified schematic representation of fronto-subcortical circuits
Simplified scheme according to Cummings 1993 and Klempir, 2007 showing the fronto-subcortical circuits: a) Dorsolateral circuit, b) orbitofrontal circuit, c) mediofrontal (anterior cingulate) circuit (Cummings 1993 and Klempir, 2007).

7. Clinical Manifestation of Huntington Disease

The main pathognomonic areas underlying the clinical presentation of HD relate to deficits in motor, cognitive, behavioural, and metabolic domains (Bates et al., 2015). The mechanism explaining which area might be affected during the disease is not fully understood and varies widely among individuals. At the onset of the disease, not all of the symptoms are necessarily clinically apparent. However, as the disease progresses, a typical clinical picture develops, but the nature and intensity of individual symptoms may vary. Clinical onset, presentation and progression of HD are determined primarily by the number of CAG triplets (Andrew et al., 1993, Duyao et al., 1993, Snell et al., 1993). HD displays a high level of clinical heterogeneity, even within families, concerning the balance of motor, cognitive, psychiatric, and metabolic features. Given this wide variation in different symptoms occurring at different times, many clinicians refer to HD as a disease of 1000 faces. The description below focuses on the most common clinical features of HD in the different domains. However, the paediatric and juvenile HD needs to be considered separately due to the different phenotypic presentations as HD in adult-onset.

7.1. Adult Form of Huntington Disease

The adult form of HD is the most common (up to 90%), with a clinical onset between 35-50 years of age (Read, 1993). Typically, the first manifestations usually occur with non-specific psychiatric and cognitive changes. However, these symptoms may facilitate the diagnosis of HD only in case of positive family history. Otherwise, the diagnosis is confirmed in most cases by the appearance of motor symptoms in terms of involuntary choreatic (jerky) movements on the distal parts of the body. In the more advanced stages, dystonia and sometimes myoclonus may occur. As the disease progresses, the hyperkinesia gradually diminishes, and an akinetic rigid syndrome develops the so-called Westphal form. Even in the early stages, bradykinesia and initiation impairments are typical (van Vugt et al., 1996). Other early neurological signs include disturbances in eye pursuit and saccadic movements. Dysarthria and latent dysphagia are common. Patients in the moderate and advanced stages develop gait disturbances with a tendency to fall (Andrich et al., 2007). HD is also associated with weight loss, which can occur at any stage of the disease (Costa de Miranda et al., 2019). The cause of weight loss is not fully understood. It occurs despite increased caloric intake and is not proportional to dysphagia or the intensity of involuntary movements (Mochel et al., 2007). Advanced and terminal stages include incontinence, severe dysarthria to anarthria with dysphagia, cachexia, akinetic syndrome and severe dementia. The patients are dependent on the

care of others. Most often, patients die from complications of infectious diseases. The average survival time is 15-20 years.

7.2. Paediatric and Juvenile Huntington Disease

Paediatric or juvenile HD (JHD) was first described by the German doctor Hoffmann from Heidelberg (Hoffmann, 1888). This disease variant affects about 5% of all HD cases (Quarrell et al., 2019). The incidence of Huntington disease before the age of 10 is around 2% (Van Dijk et al., 1986). It affects children and adolescents under 20 years of age, who usually have inherited more than 60 CAG repeats (Quigley, 2017); more about CAG repeat length in JHD is written in section 3.2.

The clinical presentation has a special characteristic and differs from an adult-onset disease. Rigidity, bradykinesia, and akinesia are present from the onset, with less hyperkinetic movements (Achenbach et al., 2020b). Other manifestations of motor impairment include dystonia, myoclonus and pyramidal symptoms(Quarrell et al., 2013). Young patients who appear to suffer from intellectual and behavioural disorders may experience learning difficulties and behavioural problems at school as a very early symptom of JHD (Chuo et al., 2012). However, the neurological symptoms may follow with a delay of several years. In adolescence, attention and learning difficulties, depression, aggression and psychotic symptoms are often mistaken for symptoms of schizophrenia (Quigley, 2017). Epileptic paroxysms of various types (grand mal, tonic-clonic, absence) occur in 30-50% of patients (Quarrell et al., 2013). As the disease progresses, patients experience rapid development of severe cognitive decline and dementia syndrome. The average survival rate is around 8-10 years (Quarrell et al., 2019). This severe phenotype of HD is also called the Westphal or akinetic-rigid variant.

7.3. Late-Onset Huntington Disease

The late-onset form (senile form) of HD is considered to have a clinical onset after the age of 60 and occurs in approximately 5% of all cases. This form of the disease has a relatively benign course, and most patients live to the average age of the healthy population. The predominant and frequently initial symptom is chorea, whose distribution and character is not different from the classical form of the disease but is less intense and slower to progress. Neuropsychological examination in most cases will show isolated cognitive deficits (especially attention-deficit and dysexecutive syndrome). However, severe dementia is rare in behavioural disorders, the most common: apathy, depression, and irritability.

7.4. Motor Symptoms

Huntington disease is characterised by involuntary movements, most of the choreatic type. The voluntary movements and corresponding motor skills are less pronounced but still very significant in the clinical picture (Long et al., 2014). In this way, the motor symptoms present in the course of HD in two phases, initially with the hyperkinetic phase with a prominence of chorea in the early stages, which tends to attenuate and plateau in more advanced HD, followed by the hypokinetic phase defined by bradykinesia, dystonia, balance, and gait disturbance (Dorsey, 2013). As the disease progresses, problems with gait and falls are present, mostly due to bradykinesia, akinesia, dystonia and impaired postural reflexes. Motor symptoms can also rapidly deteriorate in intercurrent infections, stress, and anxiety, but this is usually temporary (Ghosh and Tabrizi, 2018).

7.4.1. Chorea

Chorea is an abnormal involuntary movement derived from the Greek word "dance". It is characterized by brief, abrupt, irregular, unpredictable movements. In milder cases, chorea may appear purposeful. The patient often appears fidgety and clumsy (Long et al., 2014). In adults, chorea is the most common motor feature at the onset of the disease. It occurs predominantly in involuntary movements of the facial muscles and distal extremities, especially the fingers and toes (Roos, 2010). Overall, chorea can affect various body parts, interfere with speech, swallowing, posture and gait, and disappear in sleep. These choreatic movements are arrhythmic and jerky. In the beginning, they are mild and are unconsciously integrated into the voluntary movements, so that they are often misinterpreted as restlessness or nervousness (Reetz et al., 2015). Since the choreatic movements cannot be suppressed voluntarily, chorea is most often observed when the affected person is asked to rest or is highly concentrated on a specific (e.g. cognitive) task (Reetz et al., 2015). Surprisingly, unawareness of chorea by the patients themselves can last quite a long time and is still present in almost 50% even when the symptoms can no longer be missed by family members (McCusker and Loy, 2014b). The axial musculature is also successively affected, especially in the trunk. The further progression of the chorea with an increase in both the intensity and amplitude of the involuntary movements led to the secondary problems, but serious problems in everyday life, such as progressive imbalance, unsteady walking and frequent falls (Andrich et al., 2007). Involvement of the diaphragm and muscles in the larynx and pharynx leads to breathing problems, dysphagia, dysarthria and involuntary vocalisation with interruption of speech melody (Hamilton et al., 2012a). In advanced stages of HD, the chorea may plateau or decrease and is gradually replaced by stiffness and Parkinsonian-like features (Dorsey, 2013).

7.4.2. Dystonia

Most patients with manifest HD suffer from different degrees of dystonia, mostly occurring in the later disease stages. In general, dystonia involves inappropriate and sustained muscle contractions due to loss of coordinated contraction of antagonistic muscle groups, which alters muscle tone and leads to abnormal movements and postures, such as torticollis (neck rotation) (Albanese et al., 2011). The recent investigation by Zande et al. confirmed the high prevalence of dystonia in HD, mostly in upper extremities, in more advanced stages, correlating with disease duration (Van De Zande et al., 2017). The most prevalent type of dystonia is internal shoulder rotation, in more than half of cases followed by sustained fist clenching, excessive knee flexion, and foot inversion(Louis et al., 1999). There are more than two types of dystonia in most patients, meaning several body regions. In the average patient, three to four types of dystonia present, in the different severity from mild to moderate and in more than half of the time (Louis et al., 1999). Despite this, dystonia remains difficult to assess in the presence of chorea and tends to be overlooked in HD in favour of treating the chorea (Van De Zande et al., 2017). It is common in higher CAG repeat length, such as in paediatric and juvenile HD (Quarrell et al., 2019). Dystonia is causing functional problems in everyday life (Achenbach et al., 2020a).

Moreover, dystonia and rigidity have stronger relationships with functional status than chorea in persons with HD (Carlozzi et al., 2019). Dystonia may worsen under antipsychotic medication. Dystonia is widely considered to be a neuronal circuit disorder involving the basal ganglia, striatum, cerebellum, and primary and supplementary motor cortices (Niethammer et al., 2011). However, the pathophysiological mechanism remains unknown, and the recent animal studies indicate that loss of striatal interneurons is an underlying cause of dystonia in HD (Reiner et al., 2013).

7.4.3. Rigidity

Rigidity or hypertonia is a common muscle tone disorder in which there is resistance to passive movement irrespective of posture and velocity. It is one of the key features of HD and is usually present in other extrapyramidal disorders, such as PD (Long et al., 2014). Earlier neurophysiological observations have demonstrated excitability changes in cortical and subcortical pathways, as demonstrated by abnormalities in long-latency stretch reflexes and stretch-induced co-activation of agonist antagonistic muscles (Bologna and Paparella, 2020). In HD, is rigidity present in advanced stages and worsen with the disease progression. Rigidity in HD predominates the clinical picture in the so-called akinetic form, although it may also be present to a variable extent in the hyperkinetic predominant type. Although rigidity correlates with higher HD severity, it may significantly vary within and among patients.

7.4.4. Bradykinesia and Akinesia

Bradykinesia belongs to the common symptoms of HD. All levels of voluntary movements are progressively affected, including sensory presentation, planning, initiation, execution, and movement termination (van Vugt et al., 1996). The deficit is manifested clinically as impaired initiation of voluntary movement (akinesia), slowed movement (bradykinesia), reduced range of movement (hypokinesia), and inability to maintain a steady position (persistence). Dyskinesias also impair voluntary movements. The interference of involuntary movements with voluntary movements may worsen voluntary movements. However, bradykinesia is the most reliable marker of progenesis (van Vugt et al., 1996, van Vugt et al., 2004). Both dystonia and bradykinesia contribute to an increased risk of falls, as well as causing an increased level of accidents due to delayed responsiveness in dangerous situations (Louis et al., 1999). The care of HD patients is even more complicated as the motor dysfunction is usually accompanied by other symptoms such as deficits in postural control, generalised slowing of psychomotor function and cognitive decline (Hart et al., 2013b).

7.4.5. Eye Movements

The pathological findings occurring in the eye movements can be early symptoms and have been described in premanifest HD gene carriers. Abnormalities in the eye movement provide a distinct finding in the clinical evaluation of manifest HD, as the patients in all disease stages demonstrate a broad range of eye movement abnormalities, including impairment of pursuit, saccades, optokinetic response, and fixation (Blekher et al., 2004, Blekher et al., 2006). Therefore, special attention should be paid to examining eye movements during the neurological investigation (Blekher et al., 2004, Blekher et al., 2006).

7.5. Peripheral Disturbances

Although HD is primarily a disease of the CNS, it is known that huntingtin protein is also expressed in the peripheral cells throughout the body, resulting in a variety of peripheral symptoms (van der Burg et al., 2009). From this perspective, it is also important to consider the peripheral or metabolic symptoms in the management of HD.

HD patients can experience impairments in energy imbalance and affect food intake and absorption, causing weight loss and malnutrition and impairing the interactions among metabolic systems, thereby inducing more global energy deficits that, ultimately, may adversely impact CNS functioning (Wang et al., 2014). The metabolic changes with weight loss may occur already in

premanifest patients prior to the HD motor diagnosis. Therefore patients require a high-calorie intake to maintain their weight (Aziz et al., 2010a, Brotherton et al., 2012). There is an association between a higher body mass index at disease onset and a slower rate of disease progression (Myers et al., 1991). Other peripheral symptoms include changes in body composition, including mineral density and muscle composition, such as osteoporosis and skeletal muscle atrophy (Romanello and Sandri, 2015, Costa de Miranda et al., 2019). The early study from the USA showed that cardiac failure occurs in 30% of patients compared to 2% of age-matched controls (Lanska et al., 1988). Endocrine dysfunction in the form of impaired glucose tolerance, hypothyroidism and low male testosterone levels may occur in HD patients and contribute to the peripheral symptomatology (Aziz et al., 2010a, Aziz et al., 2010b, Ransome, 2012, Süssmuth et al., 2015).

7.6. Psychiatric Symptoms

Psychiatric complaints represent a large part of the impairments in HD. The early descriptions of HD focused more on the motor symptoms accompanied by cognitive features such as dementia. However, the psychiatric disturbances were identified very soon as a part of the clinical picture in HD (Hoffmann, 1888). The psychiatric symptoms are sometimes referred to as prodromal symptoms, which may occur before the manifestation of the motor abnormalities of HD (Vaccarino et al., 2011). From clinical practice, it appears that all patients experience psychiatric complaints to some extent during the disease, either transiently or continuously present in varying degrees of severity and form during the disease. Several cohort studies estimated rates for lifetime prevalence of psychiatric disorders among HD patients vary widely between 33% and 76% (van Duijn et al., 2008, van Duijn et al., 2014). Psychiatric symptoms are thought to be more common than estimated, with up to 98% of patients showing one of the impairments in the last months shown in Figure 11 (Paulsen, 2001, Thompson et al., 2012). The different stages present different challenges. In pre-manifest patients, the problems can occur even after the predictive diagnosis, in the form of depression or later in the run-up to the onset of the disease. Symptoms include depressive moods and apathy that can persist over time and develop into severe apathy affecting daily functioning. Besides apathy as the most frequent symptom, irritability, aggression, and obsessive-compulsive behaviour (OCD) are prevalent in all stages of HD (Paoli et al., 2017). Apathy was the key psychiatric symptom occurring most in all stages, but typically in advanced HD stages.

There are likely multiple causes of the psychiatric disorders in HD with underlying factors including a combination of neurobiological, cognitive, psychological, social and environmental factors (Goh et al., 2018). Figure 11 shows the percentage of the most frequent psychiatric symptoms based on

the Problem Behaviour Assessment (PBA) at baseline and follow up examination (Thompson et al., 2012). Subtle, subclinical psychiatric symptoms are present in this premanifest stage of HD, approximately ten years before the HD diagnosis, suggesting these symptoms to be the earliest markers of the disease (Duff et al., 2007).

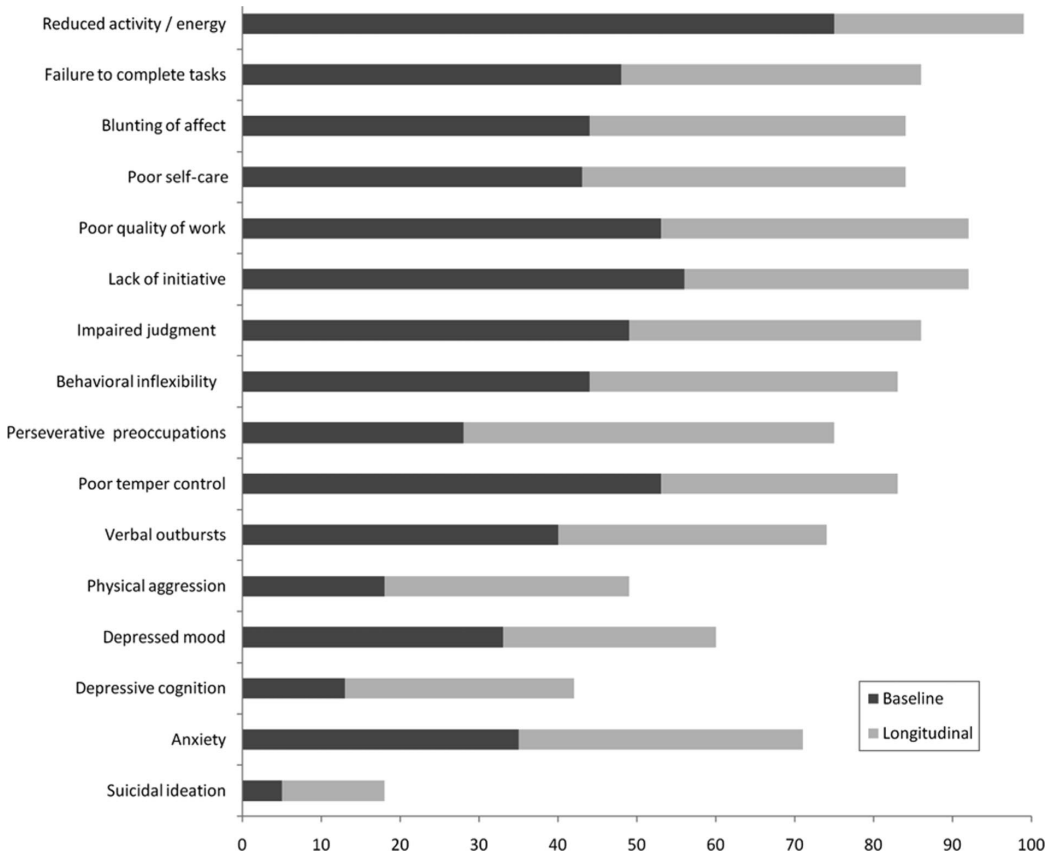


Figure 11: Psychiatric symptoms in HD
Percentage of patients endorsing each symptom on the Problem Behaviour Assessment (PBA) subscales at baseline and longitudinally: The prevalence of neuropsychiatric symptoms was notably higher in longitudinal observation suggesting overall, neuropsychiatric symptoms are very, with some symptoms occurring in 99% of patients and no single patient remaining completely free from such symptoms over the follow-up period (Thompson et al., 2012).

7.6.1. Depression and Suicide Behaviour

Depression is a common condition in HD. This condition represents a change from previous functioning to a depressed mood, loss of interest or pleasure, accompanied by sleeping impairments, weight loss due to reduced appetite, anxiety, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive or inappropriate guilt, diminished ability to think and concentrate, recurrent thoughts of death, recurrent suicidal ideation, thought of death or suicide (American Psychiatric Association, 2013). In HD, depression is associated with high morbidity, functional impairment, and a higher risk of suicidality.

It also occurs in the HD population, regardless of disease stage, both in the prodromal stage and in manifest patients, although neither the underlying mechanism nor the causes or risk factors for the development of depression are fully understood (Epping et al., 2013). Depressive symptoms were more common in HD mutation carriers, although there was no increase by approaching the onset of the disease and no association with the duration of HD (van Duijn et al., 2008). Depressive symptoms in HD are more often associated with female gender, depression in the history, and decreased functioning, but not with time since genetic testing (Epping et al., 2013). The studies in HD analysing the factors associated with depression found similar factors as in the general population, such as female gender, previous depression in the medical history and accompanying burden, such as HD (Coryell et al., 1992). Depression can contribute to significant morbidity and functional decline at any stage of disease, even in premanifest individuals (Marder et al., 2000b). Depression is also implicated in premature mortality due to suicide (Fiedorowicz et al., 2011). Particularly, the history of suicide attempts and the presence of depression is strongly predictive of suicidal behaviour in the prodromal stage (Fiedorowicz et al., 2011). The study by Baliko et al. from Hungary looked at several decades of family history and clinical information on the deceased from 96 Huntington families and found that suicide occurred most often in the early or late stages of the disease; age at onset was slightly lower in those who committed suicide than in the general population, and of the 40 people who committed suicide, 34 were men and 6 were women (Baliko et al., 2004). It implies that suicide among patients with HD is more common than in the general population. Knowledge about the high suicide risk in this disease is important for genetic counselling (Almqvist et al., 1999). The need for counselling, using a well-designed protocol, and the importance of focusing on the suicide risk of participants in predictive testing programs is emphasized (Robins Wahlin et al., 2000).

In most cases, psychiatric intervention is required, either in the form of psychotherapy or psychopharmacological support. However, it was shown that only 55% of all participants with moderate to severe depression used antidepressants, suggesting under-treatment of depression(van Duijn et al., 2014). No correlation between the presence of psychiatric symptoms and CAG repeat length has been identified (Vassos et al., 2008).

7.6.2. Apathy

Apathy is defined as a disorder of motivation with the loss or reduction of goal-directed behaviour, cognitive activity and emotions and functional impairments due to apathy (Starkstein and Leentjens, 2008). It strongly influences psychosocial functioning, including relationships with partners, caregivers, and family members (Aubeeluck et al., 2019). Sometimes it can be difficult to

distinguish apathy from the core depressive symptoms of loss of energy, depressed mood and waning interest (Watt and Seller, 1993). Apathy belongs together with depression and irritability among the most frequent psychiatric symptoms in HD, with a prevalence varying between 33% to 76% for each symptom (van Duijn et al., 2008). Many clinicians would agree that apathy causes serious problems in daily life as it affects the functionality of the affected person in the family and the provision of care in the family. Apathy is common in all stages of HD and can even be mildly present even in premanifest gene carriers and early stages of disease (Kingma et al., 2008). Apathy worsens throughout the disease and is severely present in nearly all patients in advanced stages. It could be said that once present, it tends to persist or worsen (Thompson et al., 2012). In addition, apathy itself is negatively related to functional capacity, cognitive performance and motor impairment in HD (Thompson et al., 2012). The presence, severity, and course of apathy concerning the structural neurodegenerative processes in HD are not fully understood. The neuropathological findings are associated with atrophy of the thalamus, suggesting that apathy has an underlying neural cause and might explain the high incidence of apathy in HD; however, no association was found between atrophy of these subcortical structures and increase in severity of apathy over two years (Baake et al., 2018).

7.6.3. Anxiety

In Anxiety, the person experiences not controlling the worry, which concentration deficits may accompany, restlessness, easily fatigued, irritability, muscle tension, and sleep disturbance (American Psychiatric Association, 2013). Anxiety following depression is the second most common psychiatric condition in the general population, and similar applies to HD by being anxiety common, which has a prevalence of 40% in HD patients (van Duijn et al., 2008, Thompson et al., 2012).

Anxiety may occur during the disease and from the neurodegenerative process itself. Neither depression nor anxiety relate to the disease stage and can occur in premanifest HD (Julien et al., 2007, Thompson et al., 2012). Attention needs to be paid to the fact that besides depressed mood, there is an association between anxiety and suicidal ideation (Wetzel et al., 2011, Hubers et al., 2013). In conclusion, there are contrasting data regarding the critical stage for anxiety and depression to arise, as these symptoms are combined in most cases. Paulsen identified the moderate stage of HD as the most critical, although anxiety and depression are presented in all stages (Paulsen et al., 2005).

Moreover, some studies have reported that the disease stage in HD patients does not influence anxiety levels, contrary to depression symptoms, as depression worsen the anxiety symptoms

(Berrios et al., 2002). Some of the patients undergo medical intervention supported by the use of benzodiazepine. It is assumed that benzodiazepine seems to be an independent risk factor for suicide (Paulsen, 2001, Berrios et al., 2002, Paulsen et al., 2005, Hubers et al., 2013), so special attention should be given to the individuals suffering from depression and anxiety with the use of the above medication.

7.6.4. Irritability, Agitation and Aggression

Irritability is a common clinical problem in patients with psychiatric disorders. Irritability can be defined as a transient psychological state characterized by impatience, intolerance, and poorly controlled anger may include elements of anger, aggression and decreased impulse control (Fanning et al., 2019). At the same time, aggression is the planned or reactive expression of hostility, injury and destructive behaviour directed at others or ourselves (Snaith and Taylor, 1985). Although the term "irritability" is widely used in descriptions of patient behaviour, it is poorly defined partly due to a lack of understanding of the foundational mechanisms that lead to its manifestation (Malhi et al., 2019). However, irritability does not always result in aggressive behaviours. There is a continuum between irritable mood and violent assaultive behaviour (Snaith and Taylor1985). Studies have linked irritability and hostility to other aspects of morbidity, including reduced compliance of treatment adherence to medical treatment, suicide attempts, and violence in the previous medical history (Fanning et al., 2019). Irritability may be a part of the other psychiatric disorder, but it may also occur independently. Irritability, agitation and even aggression are common in patients with HD (van Duijn et al., 2008). Irritability without evidence of a history of similar symptoms occurs in most HD patients and appears a priori to motor symptoms in HD gene carriers (Marder et al., 2000a, Julien et al., 2007). Irritability is often the first sign of the disease in presymptomatic patients with HD. However, it can occur at all stages, more commonly in patients whose neurological symptoms have been present for 6 to 11 years (Paulsen, 2001, Thompson et al., 2012). The severity of irritability and aggression may increase as the disease progresses. The neuropathological mechanism underlying irritability and aggression was examined in several studies by Cummings, suggesting that the dysfunction of frontal-subcortical circuits with striatum results in impaired executive function, disinhibition, and apathy; contributing to the development of socially inappropriate behaviours that initially may be manifested as subtle irritability and, in late-stage disease, as aggressive behaviour (Mega and Cummings, 1994). However, the appropriate pharmacotherapy can help to modulate the symptoms,

7.6.5. Psychosis

The low prevalence of the psychotic disorder in HD may be explained by the relatively high use of antipsychotic agents during HD, also due to the other indications (van Duijn et al., 2008). The psychotic disorder includes delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence, grossly disorganized or catatonic behaviour and negative symptoms (i.e., affective flattening, alogia, or avolition) (American Psychiatric Association, 2013). As reported by some case reports, the patients suffer from a particular presentation not as typically presented in symptoms occurred by schizophrenia (Chuo et al., 2012, Grabski et al., 2012). Persisting psychotic symptoms may lead from cognitive impairment, although they tend to achieve the plateau and become less present as the disease progresses (Thompson et al., 2012). It seems that the patients with an early age at onset of HD as in JHD have an increased risk of psychoses (De Marchi et al., 1998).

7.6.6. Perseverative Behaviour

Perseverative behaviour (PB) is frequently reported in HD, as in premanifest and manifest stages (Oosterloo et al., 2019). PB is the uncontrolled repetition or continuation of a response in terms of the motor act, word expression, thought, activity, strategy, or emotion that has persisted beyond the psychological context or rationale in which it arose (Serpell et al., 2009). It occurs without the individual's full awareness or insight into their presence, and the behaviour may not be distressing (Oosterloo et al., 2019). The prevalence ranges up to 75% for PB depending on disease stage, although the premanifest subject experienced PB more often than the general population (Duff et al., 2007, Epping et al., 2017). However, a study by Anderson et al. reported that 22% of manifest patients reported PB at their first clinical visit, suggesting that these symptoms may be more common than previously recognized in the HD population (Anderson et al., 2001).

7.6.7. Obsessive-Compulsive Behaviour

Obsessive-Compulsive Behaviour (OCB) is defined by recurrent intrusive and inappropriate thoughts (obsessions) and by repetitive behaviours (compulsions) such as checking and ordering, which the patient feels driven to perform in order to reduce distress (American Psychiatric Association, 2013). A patient usually realizes that his obsessions or compulsions are excessive or unreasonable, but this is not always the case. The prevalence ranges from 5 to 52% for OCB depending on disease stage, although the premanifest subject experienced OCB more often compared to the general population (Duff et al., 2007, Epping et al., 2017) and manifest patients reporting a higher rate of OCBs compared to premanifest individuals (Oosterloo et al., 2019). It is found that patients with OCBs and PBs have a longer disease duration and had more often a

psychiatric history of the comorbidities such as depression, anxiety, psychosis or other neuropsychological deficit, and more often used psychiatric medication (Anderson et al., 2018). Many HD patients show personality changes with mental inflexibility already in prodromal and early disease stages, possibly signalling the future for OCB (Anderson et al., 2001).

7.6.8. Sleep Disorder

Sleep disturbances presented in HD are similar to those in other neurodegenerative diseases: impairment of sleep latency (difficulty falling asleep), decreased sleep efficiency (difficulty maintaining sleep), early awakening, disrupted day-night cycles, and excessive daytime sleepiness. Fatigue, apathy, slowing cognitive processing, and worsening balance lead to falls (Malhotra, 2018). The circadian rhythm disruption may also be part of medical history in many individuals with HD (Morton, 2013). The sleep disturbances may increase in severity with advancing clinical stage of disease and coexisting comorbidities such as anxiety and depression or the presence of chorea that can interfere with the onset of sleep in HD (Anderson et al., 2018). Poor sleep quality harms the psychological state and functional capacities.

7.7. Cognition Deficit in Huntington Disease

Cognitive impairment is also one of the main features of HD and is present in different severity from the premanifest stage across the disease spectrum. However, the severity, frequency, and characterization of cognitive difficulties have not been well-described. Since cognitive deterioration often begins at an early stage, prior to the onset of distinct motor signs and progresses over time, representing a severe burden for a patient, the family, and the environment. Although the severity of cognitive decline varies highly and often is not recognized by the patient, rather than partners and other family members, it generally increases while the disease progresses (Paulsen, 2011). The neuropsychological profile in premanifest and manifest HD was already described in several studies, including impairment in memory, psychomotor speed, negative emotion recognition and executive functioning (Dumas et al., 2013a). Several studies highlighted that premanifest individuals typically pronounce deficiencies in psychomotor speed, emotion recognition and to some extend in executing functioning and minor deficiencies in memory, language and global cognitive functioning domains (Dumas et al., 2013a, Paulsen and Long, 2014). In manifest HD, adequate functioning remains intact for the longest periods for language and global functional domains. However, with the disease progression, impairments in memory (especially visuospatial), psychomotor speed, negative emotion recognition, and executive functioning may be expected, resulting in dementia during end-stage HD (Dumas et al., 2013a). It is essential to evaluate the

patient on all subdomains for memory, psychomotor speed, emotion recognition, and executive functioning from the clinical perspective to assess cognition appropriately. A further explanation of the cognitive domains follows below.

7.8. Cognitive Domains in Huntington Disease

Numerous studies have shown cognitive impairment is evident before motor diagnosis, and annual cognitive decline is a robust marker of disease progression (Paulsen and Long, 2014). Motor components are given such a heavy emphasis, as they are immediately visible. However, the cognitive disorders that are not notable at the first look are critical for effective environmental functioning (Boll et al., 1974). In this thesis, the latest classification developed by the DSM-V is used to describe the domains of cognition. DSM-V defines the cognitive domains as psychomotor speed, executive functioning, memory, language, global functioning, or emotion cognition, as displayed in Figure 12 (American Psychiatric Association, 2013). In this thesis, domains are adjusted for cognitive impairments reflecting HD with emphasis on the domains for psychomotor speed, emotion recognition, as the most prominent function examined and found to be deficient. Although the classification of cognitive functions exists, cognitive processes are complicated and complex. Therefore, it is often very difficult to identify only one specific function responsible for the correct performance of a task. As a result, several functions are associated with a specific task or performance and are grouped under one term. The DSM-V diagnostic criteria seem to be more

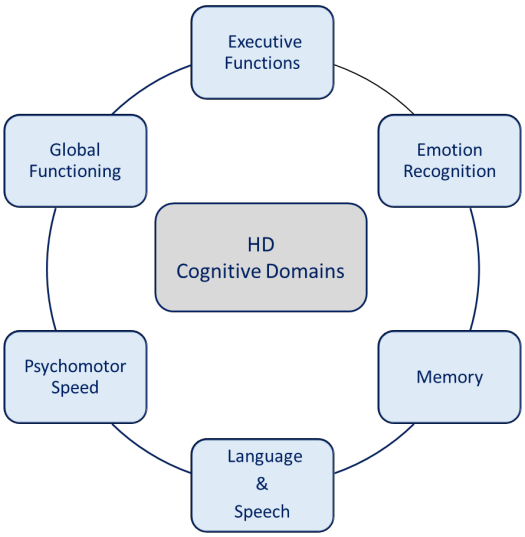


Figure 12: Cognitive domains
The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) defines six key domains of cognitive function, and each of these has subdomains. Identifying the domains and subdomains affected in a particular patient is important to assess the neurocognitive disorder's appropriate diagnosis, aetiology, and severity. Objective neuropsychological assessments are essential to be performed.

appropriate for the diagnostic and research needs in HD. The classification of the cognitive disorder is based on the impairments occurring within the six main neurocognitive domains displayed below in Figure 12.

7.8.1. Psychomotor Speed

One of the earliest and most sensitive indicators of the early signs of HD are changes in the speed of thinking and motor skills, referring to the term psychomotor speed (Beglinger et al., 2010b). The person at risk for HD notices that completing ordinary tasks is more demanding and takes more time to achieve the same result. It affects functioning in everyday life and soon at the workplace. It seems that brain processing of respective tasks that used to be automatic is slower and involves other circuits mechanism of the brain (Paulsen, 2011). This finding underlay that psychomotor processing speed is prone to detecting a cognitive deficit and progression in prodromal and manifest HD. Numerous studies confirmed the slowing of the psychomotor speed in premanifest and manifest stages of HD (Lemiere et al., 2002, Tabrizi et al., 2011, Tabrizi et al., 2012, Paulsen et al., 2014a, Larsen et al., 2015). In the case of premanifest individuals, the above studies showed that the psychomotor speed impairments are more progredient by reaching the time point prior to the disease onset (Dumas et al., 2013a). Slow psychomotor processing speed should ideally be separated from poor motor performance alone, but this is not always possible in clinical practice. As the gene carriers are labelled as manifest based on the existence of motor deficits for the clinical diagnosis, the impact of motor impairment on cognitive functioning is to be expected. Aron et al. distinguish between reaction time and movement time during a cognitive task to separate motor deficits from cognitive ones in HD. A separate analysis of these two constructs showed that the purely motor-based parameter, movement time, did not differ between patients and controls, however, only the more cognitively related reaction time differed between the groups (Aron et al., 2003). This suggests that the HD patients, despite their motor impairment, are slowed down mostly by their cognitive processes and not by their actual motor movements, such as hand movements.

7.8.2. Executive Functions and Complex Attention

Executive function is a generic term for cognitive functions thought to be mediated by the prefrontal cortex, such as planning, decision making, monitoring, control of action, evaluation, cognitive flexibility and set-shifting (Lezak et al., 2012). These functions are the most complex and essential for adaptation to many different situations in daily life. Therefore they involve the conceptualisation of the task, such as planning, action, and evaluation (Lezak et al., 2012). Impairment of executive functions can be debilitating and interfere with maintaining everyday functioning (Lai et al., 2018). Deficits in executive functions can also interfere with other cognitive

functions such as memory retrieval and prospective memory. Numerous studies confirmed that the executive functions are impaired in the early stages of manifest HD and are even more pronounced by the progression of disease (Marder et al., 2000b, Beglinger et al., 2010a, Duff et al., 2010a, Epping et al., 2017, Paulsen et al., 2017). The reports on executive functioning in premanifest gene carriers showed dysfunction in executive functions, suggesting subtle cognitive changes many years before the onset of motor symptoms (Robins Wahlin et al., 2007, Stout et al., 2011, Stout et al., 2012). However, Lemiere et al. suggested that some tests of executive functioning may be suitable for demonstrating differences between premanifest gene carriers and healthy controls at one point, but not for longitudinal monitoring of disease progression (Lemiere et al., 2002). Dumas et al. identified in the review that not all tests of executive functioning showed the difference to healthy controls. Therefore it is important to identify which sub-types of executive functioning are affected and further identify the impaired sub-types domains (Dumas et al., 2013a). They presented little evidence for categorization, attention, or verbal executive functioning problems, rather in visual and more general or mixed types of executive functioning in premanifest HD (Dumas et al., 2013a).

7.8.3. Loss of Insight

Another very common symptom for HD is loss of insight; this condition is also commonly present in another neurodegenerative diseases such as Frontotemporal dementia or Alzheimer dementia. Clinically, loss of insight means a denial or unawareness of symptoms or an unconcern about the consequences of symptoms, also known as anosognosia (Mendez and Shapira, 2005). Unawareness or diminished awareness is present when a patient's perception of obvious disease manifestations and impact differ from that of observers such as clinicians or family members (McCusker and Loy, 2014a). Loss of insight often accompanies HD and is recognized in the first place by close family members or partners, as it becomes obvious as premanifest patients moving toward a definitive diagnosis, experiencing symptoms and difficulties that are not aware. Some authors refer to anosognosia as a possible strategy for denial of illness and a coping mechanism (McCusker and Loy, 2014a). However, unawareness is increasingly seen as neurobiological in origin, possibly due to impaired nondominant frontostriatal pathway (Rosen, 2011).

7.8.4. Emotion Recognition

The ability to recognise emotions in others is key to interpersonal and social interactions and is important for non-verbal communication. Many studies have focused on recognising and processing canonical emotions (happiness, sadness, fear, surprise, anger and disgust) as they seem cross-cultural and have a biological basis in functional imaging (Ekman, 1976). More recently, attempts have been made to identify the neurological basis of emotion recognition using

functional brain imaging. Emotion recognition has been extensively researched in both premanifest gene carriers and patients with HD. It could be argued that emotion recognition should be categorized as a sub-domain under memory. However, the individuals with deficits in emotion recognition do remember what each emotion type means, only cannot recognise it upon presentation. Therefore it is considered a separate domain (Dumas et al., 2013a). In manifest HD, the recognition of certain emotions was found to be significantly affected; however, this does not apply to all emotions but mostly for negative emotions to be most affected, and with less evidence for deficits in recognition of positive emotions such as happiness (Sprengelmeyer et al., 1996) Calder et al. presented evidence of impairments in recognising anger, fear, and disgust across the three domains, with the most severely impaired recognition of anger. HD patients; further, they identified impairments in different subtypes of disgust impair recognised by HD patients, associated with different facial features, that healthy participants reliably associate with unpleasant tastes, unpleasant smells, and more general elaborated forms(Calder et al., 2010). Few studies have investigated the recognition of facial expressions embedded in an emotional body and scene context. In real life, all facial expressions are typically influenced by the context of the situation. Aviezer et al. used the face-in-context design to compare explicit recognition of facial expressions versus expression in the context of the situation (Aviezer et al., 2009). The HD mutation carriers showed deficits in recognising disgust and anger faces in standard emotion recognition tests. However, recognition of these emotions from non-face images was intact., these results suggest that despite their impaired explicit recognition of facial expressions, premanifest individuals show relatively intact processing of the same facial configurations when embedded in context (Aviezer et al., 2009).

7.8.5. Language and Speech

Language refers to the system of communication. Moreover, aphasia is used to describe an acquired loss or impairment of the language system following brain damage (Benson and Ardila, 1996). Aphasia can affect all functions that lead to the production or understanding of speech. An important problem arises when examining language skills in HD, as motor impairment can also lead to dysarthria, which could be mistaken for aphasia. Unclear or poorly understandable speech is unrelated to the cognitive functions required for speech production or comprehension. Therefore, it has proven crucial to distinguish between content and functional impairment when examining language skills. Only a few studies were conducted to evaluate the language function impairments to assess the cognitive decline in HD. In manifest HD, impairments in language functions have been reported cross-sectionally (Lemiere et al., 2002; Murray, 2000; Murray & Lenz, 2001) and longitudinal (Murray, 2000, Lemiere et al., 2004). In premanifest gene carriers, except for one study

(Stout et al., 2011), no differences in language function were found either cross-sectionally or overtime evaluation (Lemiere et al., 2004, Brandt et al., 2008).

In summary, the spoken language abilities of patients with HD are related to the severity of their motor speech deficits, cognitive impairments, or both. In terms of syntax, patients with HD produced shorter utterances, a smaller proportion of grammatical utterances, a larger proportion of simple sentences, and fewer embeddings per utterance than the matched healthy population (Murray, 2000). Cognitive disturbances in HD are characterized by a reduction in the speed and flexibility of mental processing and decreased attention, visuospatial function, and emotional recognition.

7.8.6. Global Functioning and Memory

Memory gives us the ability to recall previously learnt information or new information. It includes subtypes of long-term memory such as declarative memory, with subdivision of semantic memory (factual information) and episodic memory (situation-specific information related to a person's life).

In the premanifest individual or HD gene carriers, the cross-sectional studies showed significant working memory deficits compared to the healthy control population (Tabrizi et al., 2009, Stout et al., 2011). The longitudinal findings of the memory impairments involve rather small sample studies, although the working memory deficits appear as the most consistent findings(Rich et al., 1999, Watkins et al., 2000, Bachoud-Lévi et al., 2001, Soliveri et al., 2002, Lemiere et al., 2004, Wolf et al., 2009, Beglinger et al., 2010a) In the manifest HD, the most areas of memory are affected, however, there is evidence from cohort studies that the visual-spatial memory shows annually progredient decline (Tabrizi et al., 2011). The spatial memory includes the ability to learn the topographical configuration of environments, to locate objects and landmarks within environments, and to navigate from one place to another, which are important functions daily on the way to work and back home, or when shopping (Glikmann-Johnston et al., 2019). Additional studies showed difficulties in HD patients in tasks involving route learning, visual discrimination, pattern recognition, visuo-constructive abilities, and visuo-perception (Gomez-Tortosa et al., 1996, Lawrence et al., 1996, Lawrence et al., 1998). In general, these impairments of memory and learning abilities require increased attention to concentrate, leading to fatigue, failure and consequently loss of motivation, mood, and behavioural disturbances.

Patients complain about impaired ability to recall information (new names and events, time data). Mentioned impairments refer to the explicit (declarative, conscious) memory, which serves to preserve memories in time and space (episodic memory) and knowledge of the surrounding

environment and events (semantic memory). The impairment of remembering and assembling important information also contributes significantly to the inability to select and organise acquired information for further processing. Disorganisation in data processing causes impaired encoding and learning of new information. However, recognising already acquired information in HD is better than free recall (Fine et al., 2008).

The impairment of the implicit (procedural, non-declarative, unconscious) memory, i.e. unconscious motor skills learning, affects daily life. Implicit memory disorders are typical for the basal ganglia disorders in general and striatum in particular. In practice, implicit memory dysfunction manifests by impaired acquisition and retention of learned motor patterns (e.g. driving, dancing or playing a musical instrument). Interesting evidence was shown by a small study suggesting the normal implicit (incidental) motor sequence learning, whereas explicit (intentional) motor sequence learning was impaired in manifest and premanifest HD gene carriers (Schneider et al., 2010). Most studies on memory deficits have been performed on the premanifest subjects and presented that the deficits occur in most cases at the close point to the phenotypical conversion (Dumas et al., 2013b). There is also not a unique deterioration pattern to be defined for different memory subdomains, as the deficits are present in different severity in premanifest and manifest subjects (Hart et al., 2013a).

In advanced stages of the disease, impairment of basic motor skills, such as walking, dressing and eating, occur. However, long-term memory in Huntington disease is well preserved into the more advanced stages. Patients remember many events but have difficulty organizing them on a timeline. They remember the first symptoms of the disease but do not know when the disease started or how long it had lasted when employment ended. Semantic memory, whose disturbances are mainly associated with the temporal cortex, tends to be HD is preserved for a long time (Hodges et al., 1990). It is not uncommon for a patient to surprise those around him, for example, .by his knowledge of a specific topic. On the other hand, performance on semantic memory tests (e.g. picture naming) may paradoxically be reduced (Hodges et al., 1990).

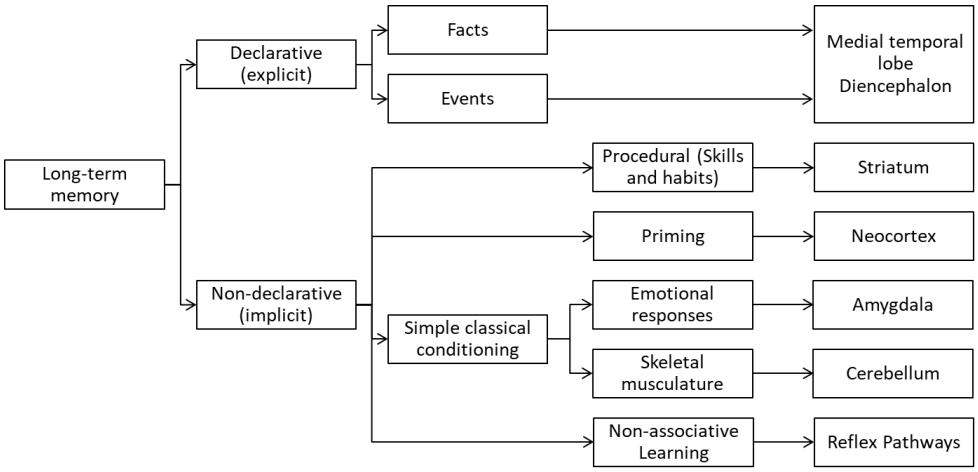


Figure 13: Long-term memory organisation.
The division into the non-declarative memory (implicit) refers to a heterogeneous collection of abilities: motor skills, perceptual skills, and cognitive skills (procedural memory) as well as simple classical conditioning, adaptation, priming, and other instances where experience alters performance independently of providing a basis for the conscious recollection of past events and declarative (implicit) resulting into the division of sematic (facts) and episodic (situations/events). Adapted from (Squire and Zola-Morgan, 1988, Ferbinteanu, 2019)

7.9. Mild Cognitive Impairment

7.9.1. Concept of Mild Cognitive Impairment

Reflecting on daily clinical practice with Huntington patients and other patient groups, there seems to be a continuous transition from the normal functioning process to the development of dementia. Presumably, there is a continuum of function between normality or normal ageing and the earliest signs of dementia, referring to the transitional condition labelled as Mild Cognitive Impairment (MCI) (Petersen, 2000). MCI is of significant importance, as one of the first longitudinal studies over two years, showed that elderly subjects with mild cognitive deficits, as determined by clinical evaluation and objective psychological testing, will develop in the further course the progressive mental deterioration with the characteristic of dementia (Flicker et al., 1991). The concept of MCI has proven valuable as it could be used to identify those who progress to dementia faster than healthy individuals of the same age (Petersen et al., 2001). We know from Parkinson research that individuals with PD may have MCI in one or more domains (Janvin et al., 2006, Aarsland et al., 2009).Figure 14 below displays an algorithm on the domain subtypes of MCI adopted from AD research. According to Petersen, MCI refers to individuals who have memory impairment greater than what would be expected for their age, with general cognitive function well preserved (Petersen et al., 1999).

The first symposium on MCI in Stockholm in 2003 proposed a general algorithm for diagnosing MCI. The classification of MCI should be gradual, considering each criterion: first, individuals should not meet the diagnosis of dementia; second, functional activities should be substantially preserved or minimally impaired; third, the person should show signs of cognitive decline as measured by either self-report and/or informant report and by the neuropsychological examination, and this cognitive decline should not be in the range of physiological ageing (Winblad et al., 2004). Already great interest was generated concerning a boundary or transitional state between normal ageing and dementia in all different types of neurological diseases with cognitive decline. It is important to consider that more than 20% of patients with MCI with primary memory impairment progress to non-AD, such as dementia with Lewy bodies, Frontotemporal dementia, progressive supranuclear palsy and vascular dementia (Jicha et al., 2006).

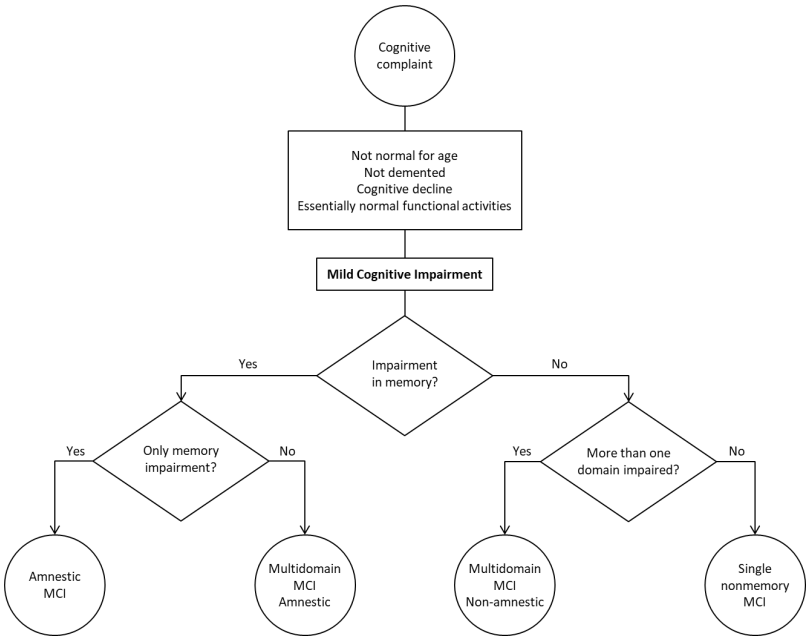


Figure 14: Mild cognitive impairment classification
The scheme is adopted from Petersen et al. (Petersen et al., 2001).

7.9.2. Mild Cognitive Impairment in Huntington Disease

There is not a clear definition of MCI in HD. In the latest approach of the DSM-V, the MCI syndrome is referred to as mild neurocognitive disorder, and the diagnostic criteria are displayed in Table 3. The diagnosis is based on the deficiency in one of the main cognitive domains described in section 7.8 (Figure 12). Duff et al. defined MCI in HD as the presence of subjective cognitive complaints and objective deficits (e.g., cognitive scores 1.5 or even more of the standard deviation on neuropsychological testing) in the absence of dementia or functional limitations (Duff et al., 2010b).

The diagnosis of MCI has gained popularity because of its utility in predicting poor cognitive outcomes. Duff et al. applied conventional criteria for MCI to a large sample of prodromal HD and reported that at least 38% of prodromal HD show impairment on standardized assessment (Duff et al., 2010a). A limitation to the concept of MCI is its broad application to AD, which cannot just be transferred to the other neurodegenerative conditions. However, many other forms of dementia can develop from this early stage of decline and need to be considered in future evaluation (Paulsen and Duff, 2009). This fact needs to be considered in the evaluation of MCI in HD. Moreover, early detection of dementia will be of critical importance in preparing for or preventing disability and efforts from delaying the onset and disease progression (Duff et al., 2010b).

The need for better detection methods for MCI in HD and other specific types of MCI is evident. The prospective longitudinal study will be essential to determine whether MCI might be a useful cognitive marker in the concept of the early detection of HD as it has proven utilitarian in other neurodegenerative disorders (Paulsen et al., 2008).

Diagnostic Criteria for Mild Neurocognitive Disorder (formerly Mild Cognitive Impairment - MCI)
I. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
II. The cognitive deficits do not interfere with the capacity for independence in everyday activities (that is, complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).
III. The cognitive deficits do not occur exclusively in the context of delirium.
IV. The cognitive deficits are not better explained by another mental disorder (major depressive disorder or schizophrenia).

Table 3: Diagnostic criteria for mild neurocognitive disorder
The diagnostic criteria as stated in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association, 2013)

7.10. Dementia and Major Neurocognitive Disorder in HD

The prevalence of cognitive decline in dementia in HD varies depending on the diagnostic criteria used, and to date, there is no unity of diagnostic criteria. Referring to the DSM V, the definition of cognitive decline has been revised, and the term major neurocognitive disorder was introduced with the impairments within the six principal domains of cognitive function that are impaired,

complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition (Figure 12). For the major neurocognitive disorder criteria based on the DSM-V, see Table 4. Peavy et al. presented that measuring and assessing processing speed, initiation, and attention better define the onset of functional decline in HD than traditional definitions established for Alzheimer's disease, which require memory deficits (Peavy et al., 2010). It can be assumed that the application of dementia guidelines developed for other neurodegenerative diseases appear not suitable for HD. Typically, HD patients have a subcortical course, generally characterised by attentional deficits, cognitive slowing, impaired planning and problem solving and visuoperceptual and constructive deficits(Salmon et al., 1989). The typical phenotype for patients with dementia of AD is cortical, characterised by memory loss, with additional changes in language, visuospatial abilities and executive functioning (Weintraub et al., 2012). Peavy proposes the following definition for dementia in HD: cognitive impairment in at least two areas of cognition in the context of impaired functional abilities and a deteriorating course but does not require a memory deficit (Peavy et al., 2010). This suggestion accurately reflects the neuropathological process underlying HD and the clinical practice and care.

Diagnostic Criteria for Major Neurocognitive Disorder (formerly Dementia)
I. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on: 1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and 2. modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
II. The cognitive deficits interfere with independence in everyday activities (requiring assistance for complex instrumental activities of daily living such as paying bills or managing medications).
III. The cognitive deficits do not occur exclusively in the context of delirium.
IV. Another mental disorder does not better explain the cognitive deficits
V. Specify: 1. Without behavioural disturbance: if any clinically significant behavioural disturbance does not accompany the cognitive disturbance. 2. With behavioural disturbance (specify disturbance): if the cognitive disturbance is accompanied by a clinically significant behavioural disturbance (for example, psychotic symptoms, mood disturbance, agitation, apathy, or other behavioural symptoms). For 3. example, major depressive disorder or schizophrenia

Table 4: Diagnostic criteria for major neurocognitive disorder
Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (2013) (American Psychiatric Association, 2013).

8. Management of Huntington Disease

The management of Huntington Disease is very important. It requires a comprehensive and multidisciplinary approach, adjusted to the patients' individual needs and depending on the stage of the disease. This section will describe the basic principles of HD management, from the diagnosis to the therapeutic pharmacological and non-pharmacological approaches in premanifest and manifest patients.

8.1. Staging System

The currently used staging system of HD is based on the patient's functional ability, called the Total Functional Capacity Scale (TFC), according to Shoulson and Fahn, which has been used in clinical practice and research (Shoulson and Fahn, 1979). The TFC score ranges between 1 and 13. It evaluates five areas concerning occupation, finances, domestic chores, activities of daily living and care level, with lower scores indicating more severe impairment of the functional status. This score builds five stages of the disease, as described in Table 5. This staging is widely used and important when describing the disease progression.

Engagement in occupation (score)	Capacity tohandle financial affairs (score)	Capacity to manage domesticchores (score)	Activities of daily living (score)	Care can be provided at… (score)
Normal (3)	Normal (3)	Normal (2)	Independent (3)	Home (2)
Reduced Capacity (2)	Requires slight assistance (2)	Impaired (1)	Needs some help (2)	Home or extended care facility (1)
Marginal work only (1)	Requires major assistance (1)	Unable (0)	Able to assist caregiver (1)	Total carefacility (0)
Unable (0)	Unable (0)		Does not participate (0)	

Table 5: The Shoulson-Fahn Staging system based on functional abilities
The scores of each domain are added to obtain the Total Functional Capacity (TFC) score. Disease stages are classified by TFC scores 11-13 (stage 1), 7-10 (stage 2), 3-6 (stage 3), 1-2 (stage 4) and 0 (stage 5) (Shoulson and Fahn, 1979).

In recent years, multiple multicentre studies of the natural history of the disease have been key to our understanding of disease onset and progression and the search for clinical and imaging biomarkers. The largest study to date is REGISTRY, a European study in 16 countries with over 17 000 participants collecting motor, cognitive and behavioural data as well as biospecimens (Orth et al., 2010), now followed by the worldwide observational study Enroll-HD (Landwehrmeyer et al.,

2016, Sathe et al., 2021). Above mentioned cohort studies contributed to the characterisation of HD's phenotype and genotype and helped foster a better understanding of the condition and its management. The important terminology has been defined to unify the description of HD. The term ''disease onset'' or ''onset of manifest HD'' refers to a patient's condition that develops classic motor symptoms of HD, which have no other explanation (Paulsen et al., 2008). Before this point, the patients may suffer from the prodromal phase of HD for many years, including subtle motor signs, psychiatric and cognitive changes (Tabrizi et al., 2011). The natural history of HD is displayed in Figure 15. Corresponding neurobiology changes occur within this period, involving loss of the cortico-striatal network and leading to striatal atrophy, which imaging techniques may detect, usually MRI (Paulsen et al., 2014a). Prior to developing manifest HD, patients carrying the HD gene mutation are referred to as "pre-manifest". For about 10-15 years before the onset of the disease, pre-manifest patients are indistinguishable from healthy individuals. However, as the onset of the disease approaches, patients are no longer completely asymptomatic. For this reason, the term "pre-manifest" may also be used by clinicians to describe those patients who suffer from prodromal HD symptoms and are likely to develop the specific motor signs of manifest HD shortly (Paulsen et al., 2008).

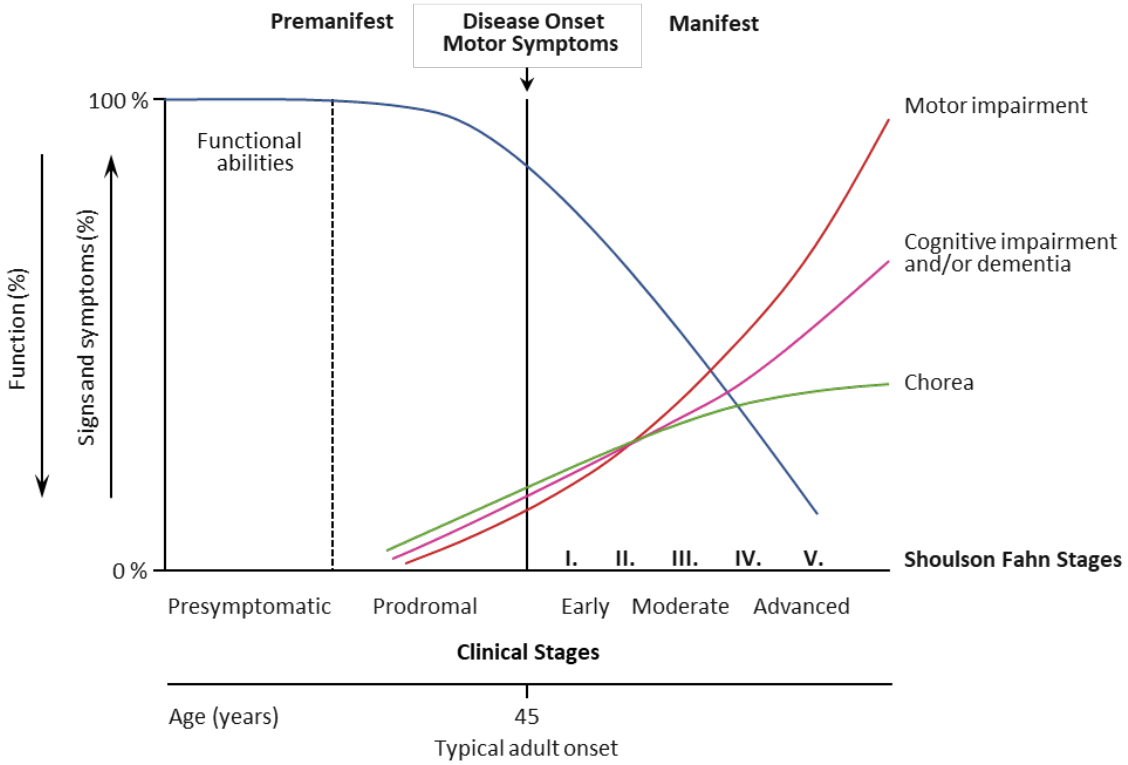


Figure 15: Natural history of HD
The period before signs and symptoms of HD appear called "pre-manifest". During the "pre-symptomatic" period, no signs or symptoms are present. In "prodromal" HD, subtle signs and symptoms are present. Manifest HD is characterised by a slow progression of motor and cognitive difficulties, with chorea often appearing early but attenuating in advanced stages (Ross et al., 2014).

8.2. Diagnosis

8.2.1. Clinical Findings

The clinical findings, including definite motor signs and behavioural impairments, combined with a positive family history for HD with an autosomal dominant transmission pattern, are suggestive of the diagnosis of HD. It is important to review the family history during the medical consultation. Figure 16 shows an autosomal dominant transmission in a Bavarian family over four generations. If there is no family history available, the evaluation of other clinical signs and symptoms must be considered carefully if the clinical picture is consistent with HD. In some cases of family history, the HD can be misdiagnosed under the other neurological condition, such as Parkinson Disease (PD) or dementia. As HD is an autosomal dominant disease, each sibling of an affected individual has a risk of 50% to be a gene carrier of the *HTT* gene. The diagnosis of HD can be confirmed through genetic testing to determine CAG repeat length.

8.3. Genetic Testing

The first genetic test using linkage markers was performed in 1983 (Gusella et al., 1983). However, these predictive tests were part of research protocols that included extensive genetic counselling. Investigators were concerned about the potential adverse psychosocial effects of revealing to individuals their almost certain risk of carrying the gene for a fatal untreatable disease (Nance, 2017). Soon after identifying the *HTT* gene, a simple and accurate blood test became available in clinical practice. The first guideline for genetic testing and counselling was established (Nance, 2017). The guidelines for genetic counselling have been established (Nance et al., 1998), but the standard guidelines have been established for the technical laboratory procedure(Potter et al., 2004). In the gene blood test, the measurement of CAG repeats length functions as a trait marker rather than a condition marker, meaning that the genetic test can be used either to confirm a clinical diagnosis of HD in symptomatic individuals or to predict whether or not an at-risk individual will develop HD later in life (Craufurd et al., 2015). The requirements for genetic counselling differ for diagnostic and presymptomatic (predictive) testing. Predictive testing is governed by precise guidance on the content of counselling and the performance of genetic testing (Macleod et al., 2013). The variety and complexity of clinical situations in which diagnostic genetic testing for HD may be required and differential diagnosis make it impractical to establish guidelines such as those for predictive testing (Craufurd et al., 2015).

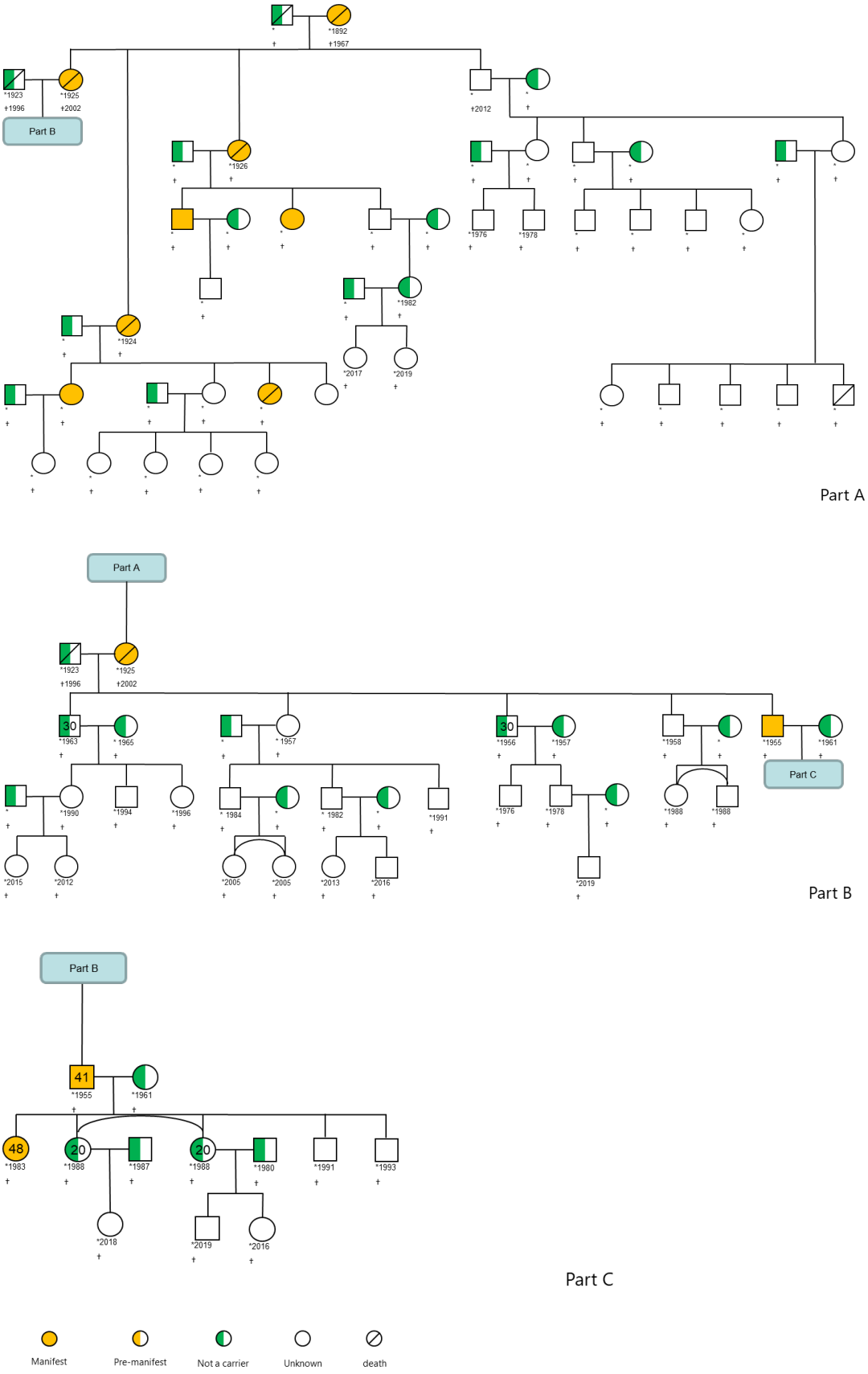


Figure 16: Pedigree chart of a Bavarian family
Family history evaluated in the pedigree of a Bavarian family and displayed in 4 generations, showing a typical autosomal dominant pattern. Each sibling of an affected individual has a risk of 50% to be a gene carrier of the HTT gene.

The most important in predictive and diagnostic genetic testing procedures are appropriate counselling. Informed consent from the patient must be obtained before testing. The implications of a positive result for the patient and their family must be clearly outlined, and both the nature of HD itself and its autosomal dominant inheritance must be explained to make it clear that if the test is positive for HD, any of their children would have a 50% chance of inheriting it.

8.3.1. Imaging Methods

The additional investigations, such as imaging and laboratory testing, including Cerebrospinal Fluid (CSF) analyses, do not currently play a key role in diagnosing HD, other than to rule out alternative diagnoses in case of choreatic syndromes (Ghosh and Tabrizi, 2018). Over the past years, neuroimaging techniques such as Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) have provided important advances in our understanding of HD by providing information about the structural and functional organization of the basal ganglia and other cerebral structures (Georgiou-Karistianis et al., 2013, Niccolini, 2014). Although imaging methods are not required to diagnose HD, they are rather needed in the case of differential diagnosis. MRI and PET can detect changes in the brains of HD gene carriers years ahead of the manifestation of the disease (Tabrizi et al., 2013a, Paulsen et al., 2014b) The structural imaging has been the source of the most robust biomarkers for HD, particularly the structural MRI have shown significant cross-sectional and longitudinal changes in volumes of the striatum, in both premanifest and manifest HD, even in those individuals who are more than 15 years from the estimated onset of diagnosable signs (Henley et al., 2009, Tabrizi et al., 2012, Rees et al., 2013, Paulsen et al., 2014a). Other regions, such as the globus pallidus, thalamus and hippocampus, also undergo atrophy, though the volume reduction in these regions is smaller than in the striatum (Paulsen et al., 2010, Younes et al., 2014). The current PET studies are assessing changes in postsynaptic dopaminergic receptors, brain metabolism, microglial activation, and recently also phosphodiesterase 10A (PDE10A) as markers to track HD progression. An overview of the available imaging biomarkers for PET and MRI is displayed in Figure 17.

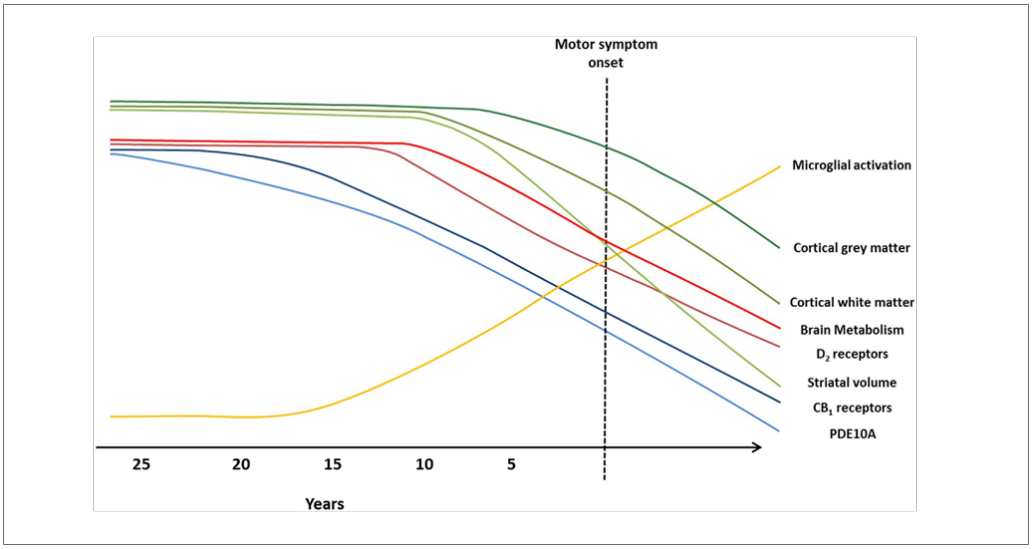


Figure 17: Imaging biomarkers PET and MRT to track HD pathology
Changes in markers represent alterations observed in MRI and PET studies and the predicted progression over the disease course., from premanifest to the manifest stage. Green lines represent MRI markers (Ross et al., 2014): loss of cortical grey matter (top, dark green), cortical white matter (middle, green) and striatal volume (bottom, light green). Blue, red and yellow lines represent PET markers; decline in brain metabolism (top, bright red), dopamine type 2 (D2) receptors (bottom, dark red), cannabinoid type 1 (CB1) receptors (top, dark blue), phosphodiesterase 10A (PDE10A) (bottom, light blue) and increased microglial activation (yellow) (Wilson et al., 2017).

8.4. Differential Diagnosis

HD classically presents with a movement disorder, cognitive dysfunction and behavioural problems but is phenotypically variable. In the clinical practice., around 1% of patients who are thought to have HD are subsequently tested negative for the HD gene mutation. These patients may have different underlying genetic mutations collectively known as HD phenocopies (Wild et al., 2008). Genetic diseases are known to cause HD phenocopies to include HD-like syndromes type 1 (HDL1) and type 2 (HDL2) and type 4 (HDL4), also known as spinocerebellar ataxia (SCA17). HD also has phenotypic overlap with dentatorubral-pallidoluysian atrophy (DRPLA), the spinocerebellar ataxias and neuroferritinopathy. Identifying the genetic basis of HD phenocopies is important for diagnosis and further managing the respective condition. An overview of the known causes of HD phenocopies is shown in Table 6.

In most cases, the genetic cause and the diagnosis remain unknown. In older people, chorea can be caused by a vascular aetiology, such as a stroke or vasculitis. However, the most common cause of chorea is of most pharmacological aetiology. It is important to consider and rule out the possible manifestation of chorea due to autoimmune diseases or infections.

Disease	Mutation
Familial amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)	C9orf72 hexanucleotide repeat expansion in chromosome 9 open reading frame 72 protein
Huntington disease-like syndrome (HDL) 1	PRNP octapeptide insertion in gene encoding prion protein
HDL2	JPH3 triplet repeat expansion in gene encoding junctophilin-3
HDL3	Causative mutation is not yet known
Spinocerebellar ataxia (SCA) 17 (HDL4)	TBP triplet repeat expansion in gene encoding TATA-box binding protein
SCA1/2/3	ATXN 1/2/3 0 triplet repeat expansion in gene encoding Ataxin-1/2/3, respectively
Dentatorubral-pallidoluysian atrophy (DRPLA)	ATN1 triplet expansion in gene encoding atrophin-1
Chorea-acanthocytosis	VPS13A mutation in gene encoding chorein
McLeod Syndrome	XK mutation in XK gene on X-chromosome, encoding a supporting protein for Kell antigen on the surface of red blood cell
Neuroferritinopathy (NBIA2)	PLA2G6 mutation in gene encoding ferritin light chain
Neurodegeneration with brain iron accumulation (NBIA1) or Pantothenate-kinase associated Neurodegeneration (PKAN)	PANK2 mutation in gene encoding pantothenate kinase 2
Inherited prion disease	PRNP mutations in gene encoding prion protein
Friedreich's ataxia	FXN triplet repeat expansion in gene encoding frataxin

Table 6: Differential Diagnosis: HD phenocopies and their corresponding genetic cause.

8.5. Therapeutic Approaches

The clinical practice has shown that the optimal management for neurodegenerative disorders such as an HD involves pharmacological and non-pharmacological interventions delivered by a multidisciplinary approach (Radder et al., 2020). However, there is no guideline specifying how this model should be organized, and the nature of multidisciplinary care varies widely (Lidstone et al., 2020).

The management and therapy of HD require a multidisciplinary team approach involving neurologists, psychiatrists, general practitioners, geneticists, psychologists, physiotherapists, occupational therapists, speech and language therapists, dieticians and nurses. In the different stages of the disease, the different team members are required for counselling and therapy (Ghosh and Tabrizi, 2018). The counselling of the caregivers or other family members is also an important part of the multidisciplinary therapeutic concept. A senior physician should lead the

multidisciplinary team, and all team members should have experience with the movement disorder, particularly HD. This is maybe best achieved through HD clinics and centres. It is also meant to work closely on the patient initiative, where representatives from local HD support groups can also provide peer to peer support and help with practical, emotional and social matters. In summary, various international and national therapeutic guidelines recommend that all patients with HD should have access to a broad range of medical and allied health professionals.

8.5.1. Pharmacological Approaches

Currently, there is no curative treatment for the disease; only symptomatic approaches are available with the aim of symptom relief or symptom control (Tabrizi et al., 2020). There are no recommendations as to when symptomatic pharmacological treatment should be started, which depends on the severity of the condition. The start of symptomatic treatment has no direct influence on the neurodegenerative process and should therefore be weighed critically and according to the patient's needs. The aim should be to ensure the best possible quality of life for a patient. The benefits and adverse effects should be assessed individually and regularly evaluated. In the early stages, pharmacological therapy should be initiated according to the patient's wishes and not be driven by the demands of relatives who, for example, feel inconvenienced by the involuntary movements or cannot bear to do anything. In contrast, the patient suffers according to their perception (Reetz et al., 2015). However, an ethical dilemma can arise at the latest when the affected person is disabled in everyday life or at work but does not want to take medication because he or she does not perceive the choreatic movements or other deficits, this is a typical feature in HD (Reetz et al., 2015 It is essential to build a relationship of trust between the patient and the doctor by regularly seeing the patient and their relatives, as well as regularly offering standardised appointments to objectify motor symptoms and functioning and discuss medication options based on comparing these results with the HD patients own perception.

Chorea should only be treated with medication when it becomes relevant and causes restrictions in everyday life. The indication for therapy depends on the circumstances, e.g. active working life; this may become necessary earlier or be postponed to a time when relevant restrictions are present, e.g. risk of falling and injury. In Germany, tiapride is widely used(al., 2017). Alternatively, tetrabenazine and other atypical antipsychotics can be used to treat chorea(Schultz et al., 2019). However, in patients with depression, tetrabenazine must be used with caution not to worsen the condition (Schultz et al., 2018).

Drug	Starting dose	Maintenance Dose	Side effects/ contraindications
Tiapride	2-3 × 50-100 mg	3 ×100-200 mg, in severe chorea. max. 3-4×300 mg	Sedation, EPMS, rarely MNS, higher doses often tolerated, but usually not more effective
Tetrabenazine	1-3 × 12.5 mg, slowly dose up	3 × 12,5 -25 mg, in severe chorea max. 3 × 50 mg.	Depression, suicidality, sedation, EPMS; rarely MNS
Sulpiride	2-3 × 50-100 mg	3 × 100-200 mg	Like tiapride
Olanzapine	2.5-5 mg/d	5-10 mg/d, max. 20 mg/d	Like tiapride
Quetiapine	2-3 × 25-50 mg	2-3 × 100-150 mg, max. 450 mg/d	Like tiapride
Risperidone	0.5-2 mg/d	1-4 mg/d, max. 6 mg/d	Like tiapride
Haloperidol	0.5-2.5 mg/d	5-10 mg/d	EPMS, rarely MNS,

Table 7: Pharmacological therapy of chorea
Recommendation based on the Guidelines for Huntington Disease from German Neurological Association, (al., 2017), Abbreviation: EPMS: extrapyramidal motor side effects; MNS: malignant neuroleptic syndrome

The management of psychiatric symptoms depends on the condition to be treated, and the pharmacological approach is mostly combined with a psychotherapeutic approach that focuses on the respective symptoms. Low-threshold Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) are commonly used for depression and anxiety disorders in HD. This SSRI may also be administered in case of irritability, impulsivity and aggression in the first line, followed by the atypical antipsychotics (olanzapine, risperidone).

8.5.2. Future and Gene Modifying Therapies in HD

There is an urgent and unmet need for treatment that slows the symptoms of HD in mutation carriers and thus prevents the onset of the disease. Several promising approaches for HD are designed to modify the natural history of HD. are currently under investigation in research studies and clinical trials. The aim of these new treatment strategies is to reduce the reproduction of mutant Huntingtin (HTT) gene products. For the first time, concrete hopes arise that intervention at the beginning of the chain of pathogenetic events can have a clinically significant, disease-modifying effect and slow down HD's so far relentless progression. Currently discussed therapeutic strategies include the degradation of mRNA species coding for HTT, either by antisense oligonucleotides (ASO), RNA interference-based approaches or orally available, small molecular splice modulators, as well as the suppression of HTT gene expression by zinc-finger protein repressor complexes up to genome editing by the CRISPR/Cas9 system (Mühlbäck et al., 2020)

8.5.3. Non-Pharmacological approaches

The non-pharmacological approaches are of the same importance as the pharmacological intervention. Several approaches have been evaluated implemented in clinical practice.

Particularly, physiotherapy is useful to optimize gait and balance for as long as possible, reduce falls and maintain the physical condition. It also helps to improve the psychical condition. In the later stages, the physiotherapy focused on dystonia and rigidity and in later stages can offer walking aids if needed (Dempster et al., 2015).

Occupational therapy is very helpful in adapting the home environment to the affected person's needs. These therapists are able to practice activities for long-term independent functioning and develop strategies that increase safety and allow patients to live and be cared for at home longer (Cook et al., 2012).

Speech and language therapists can improve communication and provide exercises to maintain good swallowing functioning. In advanced stages, special communication aids, such as communication cards, pictures and speech computers, can be adapted according to the patient´s condition (Hamilton et al., 2012a). They can also assess swallowing and advise on an appropriate diet. Some countries work closely with nutritionists to provide the best nutrition care. In the case of dysphagia in advanced HD, enteral nutrition via a gastrostomy may be needed to maintain adequate nutrition (Hamilton et al., 2012b). The feeding tube may be inserted as a percutaneous endoscopic gastrostomy (PEG). Dieticians can set up enteral feeding regimens and give more specialist advice on high caloric supplementation and rich in vitamins and micronutrients (Stratton et al., 2004). It is very important to provide appropriate counselling by social workers who can support the affected families in terms of care planning and practical organization to coordinate the move to a residential or nursing home, if necessary.

Psychotherapy in the context of Huntington's disease is a very broad field that has gained importance in recent years. In principle, all individuals affected by Huntington's disease can benefit from psychotherapy. The goals to be achieved with psychotherapy are very different and individual. They are discussed and determined together with the psychotherapist. They can range from support in decision-making, e.g. in the case of a genetic test or a professional decision, to improving coping with the course of the disease, improving depression or anxiety therapy, or coping with the crisis of suicidal thoughts (Anderson et al., 2018).

8.5.4. End-Stage Disease

As Huntington disease is progressive, end-of-life care is important for all patients. Although this topic can be difficult, preliminary discussion of these issues is very important, particularly as long as the patient can still make decisions before significant cognitive or psychiatric deterioration occurs. The important issues are oral feeding, which can become complicated with swallowing as dysphagia progresses, leading to acute life-threatening situations with choking or repeated aspiration pneumonia. Some patients may wish to receive enteral feeding via a feeding tube under these circumstances; others wish to refrain from these measures. Special point support with an appropriate nutritional regime is required to maintain oral nutrition.

The most frequent primary causes of death in HD patients are aspiration pneumonia due to severe dysphagia and cardiovascular diseases (Sorensen and Fenger, 1992). Suicides accounted for 5 % of all deaths among the HD subjects, significantly higher than the corresponding frequency of 2.7% in the general population(Sorensen and Fenger, 1992). The different comorbidities that may accompany the advanced stages of HD, such as neurological or metabolic diseases, were reported with an increased frequency in the HD patients compared to the general population, 6% versus 1% (Lanska et al., 1988).

Furthermore, it is important to discuss the situation and course of action in medical emergencies, potentially fatal, such as aspiration pneumonia, infections, sepsis, accidents and serious falls with consequential injuries. It is important to discuss the level of care they would receive regarding antibiotics, hospitalisation and resuscitation. In many European countries, patients can draw up an advance directive specifying the care they would receive in certain circumstances if they lose their capacity to act. Alternatively, patients can give a power of attorney to a person who can make decisions on their behalf if it becomes necessary. These decisions must be made in either case while the patient can still do so. Home care may no longer be possible with advanced illness, and a residential or nursing home may become necessary. Some patients prefer to be cared for at home or in a hospice at the end of life. With the support of community palliative care teams, community nurses, general practitioners and family doctors, end-stage care can also be very well provided at home, according to the person's wishes.

II. Assessing Cognition in HD: the Relationship between Cognitive Performance, Functional Decline and Disease Burden

1. Study Aims and Hypothesis

Cognitive decline is a major feature of Huntington disease. Therefore, it is crucial to evaluate cognitive decline with an appropriate approach consisting of specific and sensitive methods. An evaluation of cognitive impairment over time in a person with Huntington's disease can be performed with neuropsychological diagnostics, consisting of assessments for monitoring disease progression and evaluating functional abilities.

Over the decades, a variety of cognitive tests have been used to assess the cognitive decline in HD, including screening tools such Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Further, the Unified Huntington's Disease Rating Scale (UDHRS), a clinical scale developed by the Huntington Study Group, with a final version introduced in 1996, may assess four main domains affected in HD such as motor function, behavioural abnormalities, functional capacity and cognitive function (Huntington Study Group, 1996). The UHDRS is widely used in research and clinical practice. Particularly, the cognitive battery of the UHDRS comprises the following neuropsychological tests: Letter Fluency Test (LFT) (Benton and Hamsher, 1976), Symbol Digit Modalities Test (SDMT) (Smith, 1982), Stroop Tests consisting of Stroop Word Reading Test (SWRT), Stroop Colour Naming Test (SCNT) and Stroop Interference Test (SIT) (Stroop, 1935, Golden, 1978). Several early studies identify these assessments as the most appropriate neuropsychological tests to identify early cognitive deficits in prodromal and early stages of HD (Queller, 2008).

Further, the additional neuropsychological tests, such as Trail Making Test A and B (TMT-A and TMT-B) (Reitan, 1958), Categorical Fluency Test (CFT) (Benton and Hamsher, 1976) and Mini-Mental Status Examination Test (MMSE) (Folstein et al., 1975) have been added to the UHDRS cognitive battery to create the Enroll-HD cognitive battery, that was examined and studied in this study.

Overall, the Enroll-HD cognitive battery consists of SDMT, Stroop tests, TMT-A and TMT-B, Letter and Verbal Fluency Test, and MMSE in the final version. This structure is the Enroll-HD cognitive

battery suitable for screening for cognitive decline and continuously monitoring HD patients in prodromal and manifest stages. It includes neuropsychological tests for key cognitive domains that are sensitive indicators of HD progression, i.e., psychomotor and processing speed, attention, working memory and executive functions. Moreover, this cognitive battery is well established in clinical practice, and it is an essential tool for monitoring cognition in observational studies and clinical trials.

The main objective of the present study was to examine the diagnostic accuracy of the Enroll-HD cognitive battery consisting of the Symbol Digit Modalities Test (SDMT), Stroop Color Naming Test (SCNT), Stroop Word Reading Test (SWRT), Stroop Interference Test (SIT), Letter Fluency Test (LFT) and Categorical Fluency Test (CFT), Trail Making Test A (TMT-A) and B (TMT-B) and MMSE.

Further, this study aimed to investigate if the Enroll-HD cognitive battery is sufficiently specific and sensitive to discriminate normal cognitive functioning in healthy controls from cognitive deficits in HD patients and differentiate HD patients with more and less pronounced cognitive deficits. The less and more pronounced cognitive impairment classification was based on the MMSE cut-off score of 27 for global cognitive functioning.

In addition, the study aimed to explore the effects of disease burden on the cognitive performance of HD patients and examine the relationship between cognitive, motor and functional status. This study looked closely at the relationship between cognitive decline, age and genetic load. The evaluation of the diagnostic accuracy is essential as it allows clinicians to interpret the results obtained by HD patients in neuropsychological tests. It will enable the cognitive status to be assessed and the patient and their caregivers to be informed of the degree of current cognitive dysfunction (i.e., mild, moderate, severe). This can be useful for evaluating and monitoring the quality of life of those affected by HD and planning future disease-modifying therapies.

2. Methods

2.1. Study Design

In this prospective observational study, a total of 256 participants were recruited between 2011 and 2017 at the Huntington Centrum South, Isar Amper Klinikum, in Taufkirchen (Vils), Germany. This study was conducted in the framework of an international observational Enroll-HD study.

Enroll-HD is a global clinical research platform designed to facilitate Huntington's clinical research and support the regional research project. In the context of the Enroll-HD study, the phenotypical data are collected longitudinally on an annual basis (Sathe et al., 2021).

The local institutional ethical review board has approved the Enroll-HD study. All study procedures were conducted in accordance with the ethical standards described in the Declaration of Helsinki of 1964. All participants provided written informed consent for their participation. Any information that could disclose the identity of the examined subjects was omitted.

2.2. Study Procedure

2.2.1. Study Participants

For this study, the following participants' cohorts were created: (I) Manifest carriers of the HD expansion mutation gene referred as to manifest HD patients (mHD) and (II) Healthy Controls (NC). Only participants that met the predefined inclusion criteria as listed below were enrolled on this study.

Additionally, it was required that all subjects must be able to understand and complete a neuropsychological assessment (study assessment) independently (as judged by the clinician). Additionally, they were the first speakers in the conducted language, the German language. Individuals with severe cognitive impairments or any present psychiatric, neurological, sensory, metabolic deficits, or other disorders that interfere with the assessment administration were excluded. Moreover, minors (age < 18 years) or participants who could not provide informed consent were also excluded.

In the following section, the inclusion and exclusion criteria for both participant cohorts are described in more detail:

Inclusion Criteria

All participants (independent of the study cohort) were eligible if they met the following inclusion criteria:

i. Are ≥18 years of age,
ii. Are first language speakers in the German language,
iii. Are capable of completing the study assessment,
iv. Are capable of providing informed consent.

For the manifest HD patients study group (HD), participants additionally must meet the following criteria:

i. Have a local genetic test confirming a CAG expansion ≥ 36 in the huntingtin (*HTT*) gene,
ii. Have clinical diagnostic motor features of HD, defined as UHDRS Diagnostic Confidence Level (DCL) Score < 4,
iii. All patients undergoing therapy were given long-term continuous medication at the time of the examination.

For healthy controls (NC), participants additionally must meet the following criteria:

i. No cognitive impairment, defined as MMSE ≥ 27.

Exclusion Criteria

All participants were ineligible (independent of the study cohort) if they met any of the following exclusion criteria:

i. Minor subjects (age <18 years); or
ii. Individuals with any present serious psychiatric, neurological, sensory, metabolic deficits or any other disorders that are known to be of a significant influence on patient's or healthy control and therefore likely to influence the answers on neuropsychological assessment; or
iii. Persons who are unable to provide informed consent.

The healthy control participants were ineligible if they additionally met the following exclusion criteria:

i. Individuals diagnosed with manifest HD or carriers of the HD expansion mutation gene.

As mentioned above, the study enrolled in two cohorts, manifest patients (HD) consisting of 106 patients (52 males and 54 females). The control group (NC) consisted of 100 healthy volunteers (39 males, 61 females) who matched the patient group regarding age, gender and education level.

2.3. Study Assessemnts

The following section describes the study procedures and assessments performed in the study in detail. An overview of the study assessments can be taken from Table 8 below.

Study Assessments	
Enrolment Procedure	Inclusion and Exclusion Criteria Review
Sociodemographic Information:	Age Genetic Test (CAG) Disease Burden Score (DBS) Date of Test Date: HD clinical diagnosis Ethnicity Gender Marital status Living & caring situation Employment status Years of education
Medical history:	Comorbidities
Current HD-related Therapies:	Pharmacotherapy Nutritional Supplements Non-Pharmacologic Therapies
Functional Assessments:	UHDRS Total Functional Capacity UHDRS Functional Independence Scale
Motor Assessments:	UHDRS Total Motor Score UHDRS Diagnostic Confidence Index
Cognitive Assessment:	Symbol Digit Modalities Test Stroop Colour Naming Test Stroop Word Reading Test Stroop Interference Test Categorical Verbal Fluency Letter Verbal Fluency Trail Making Test A Trail Making Test B Mini-Mental Status Examination

Table 8: Study assessments overview
Note: UHRDS: United Huntington Disease Rating Scale. The number of CAG triplets (Cytosin, Adenosine, Guanin) referred to the severity of HD.

2.3.1. Recruitment and Informed Consent

This section describes the general procedure for identifying the eligible participants, providing participant information and obtaining informed consent. Participation in this study was offered to suitable individuals during their visits at the clinical site of the Huntington Centre South in Taufkirchen. The identification of potentially eligible participants was guided by the locally held

patient's database Enroll-HD. By filtering the database by the respective inclusion and exclusion criteria (as detailed in section 2.2.1). The clinic participants were approached and asked about the possibility to participate in the study in the context of scheduled Enroll-HD visits.

Furthermore, the locally held Enroll-HD database was used as a recruitment tool to identify potentially eligible participants in each of the two participant cohorts. The potentially eligible participants were informed during their visit to the clinic about the possibility of participating in the study. Prior to any study-related activity, participants were thoroughly informed of all aspects of this study and provided their written informed consent.

2.3.2. Sociodemographic Information

For each participant who agrees to participate in the study, the following sociodemographic information was collected: age, gender, ethnicity, marital status, living and caring situation, employment status., years of education.

2.3.3. Medical History

For the study, the information on the comorbidities, including addictions and the ongoing medications, particularly pharmacotherapy, in patients with relation to HD was collected. Further considering the HD diagnosis, the date of genetic test and the estimated date of the disease onset were noted. In the genetic test, both alleles with a number of CAG were collected for the patient population.

2.3.4. Disease Burden Score

We used the Disease Burden Score (DBS) to indicate the pathological burden caused by lifetime exposure to mutant huntingtin. We used the Disease Burden Score (DBS) (Penney et al., 1997). The DBS is calculated by using the following formula:

$$DBS = (CAG_n - 35{,}5)\ x\ age$$

Equation 1: Disease Burden Score

The DBS Score is the product of age and excess of CAG-repeats. The scaled DBS score is a variable referring to time to diagnosis in a survival model containing only CAG and age (Penney et al., 1997, Ross et al., 2014). Penney et al. identified a linear correlation between the CAG repeat number and the quotient of the degree of atrophy in the striatum, a brain region most severely affected in HD, divided by age at death, with an intercept of 35.5 repeats (Penney et al., 1997). Therefore, the most

extensive CAG repeat length at which no pathology is expected to develop is 35.5. These results imply that striatal damage in Huntington disease is almost entirely a linear function of the length of the polyglutamine stretch beyond 35.5 glutamines multiplied by the patient's age (Penney et al., 1997). The CAG-repeats and DBS score was determined and documented for the patient group, not the healthy control group.

2.3.5. Functional Assessments

The functional status of the participants was assessed using two scales included in the UHDRS (Huntington Study Group, 1996), the Functional Independence Scale (UHDRS-FIS) and the Total Functional Capacity Scale (UHDRS-TFC) (Young et al., 1986, Shoulson, 1989). Both scales provide an indicator of an individual's independence in activities of daily living.

UHDRS Total Functional Capacity

Study subjects will also be classified based on the Unified Huntington's Disease Rating Scale Total Functional Capacity (UHDRS-TFC), which assesses the grade of independence and functioning in daily living (Shoulson and Fahn, 1979), based on five questions concerning occupation, finances, domestic chores, activities of daily living and care level, with lower scores indicating more severe impairment of the functional status. Detailed information on the concept of the TFC can be found in Table 5: The Shoulson-Fahn Staging system. The scores of each domain are added to obtain the TFC score, grouped into five stages, starting with stage 1 with the TFC score between 11 and 13 points; those are minimally affected subjects (Early HD), up to stages 2 and 3 (Moderate HD) and severely affected individuals with a TFC score below 5 points (advanced HD) (Shoulson and Fahn, 1979, Beglinger et al., 2010c).

UHDRS Functional Independent Scale

The Functional Independent Scale (FIS) score ranges from 0% to 100% based on 25 questions (yes/no), which evaluate the ability of a subject to carry out everyday activities independently. The scale provides information about a range of functional abilities that may vary from any impairment to severely impaired.

2.3.6. Motor Assessments

Total Motor Score

The complete neurological examination of the motor system includes a standardized examination according to the Unified Huntington's Disease Rating Scale - Total Motor Score (UHDRS-TMS)

(Huntington Study Group, 1996). The UHDRS-TMS is a structured scale that allows a very good assessment of the severity of motor symptoms in HD patients (Mestre et al., 2018). The UHDRS-TMS comprises 15 items and has a maximum score of 124. The different items of the UHDRS-TMS are organized in the following categories: chorea, dystonia, bradykinesia, motor performance, oculomotor function and gait balance and allow calculating the separate scores. The UHDRS-TMS has been used in multiple observational studies and clinical trials beyond the group that developed it. It has been used in both premanifest and manifest HD populations.

Diagnostic Confidence Level

This assessment is part of the UHDRS-TMS and provides the Diagnostic Confidence Level (DCL) (Huntington Study Group, 1996), which indicates the certainty of HD diagnosis in the subject with motor signs of Huntington Disease. There are up to 4 points, from 0 (no abnormalities) to 4 points (symptoms that are undoubtedly signs of HD (99% -100% confidence). This score is necessary to differentiate between pre-manifestation and manifest disease stages.

2.3.7. Cognitive Battery

The cognitive state of participants was assessed by a comprehensive neuropsychological battery of the Enroll-HD consisting of the following tests: SDMT, SWRT, SCNT, SIT; CLF, LVF; TMT-A, TMT-B and MMSE. In the following, these neuropsychological tests will be explained in more detail.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) (Smith, 1982) assessed the psychomotor speed and working memory. The first digits (1-9) assigned to symbols were presented to the participants during this assessment. In the second step, the participants were required to write below each presented symbol the correct corresponding digit. The number of correct matches completed in 90 seconds was recorded.

Stroop Word Reading Test

This assessment has very good properties for detecting a cognitive decline in the early stages of HD as it measures attention and psychomotor speed. This assessment is a subtest of the Stroop tests (Stroop, 1935, Golden, 1978). During this assessment, the participant was asked to read words indicating colours (red, blue, green) printed in black ink as quickly as possible; the time limit was 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Stroop Color Naming Test

The Stroop Colour Naming Test (SCNT), as part of the Stroop tests, has very good properties for detecting a cognitive decline in the early stages of HD as it measures attention and psychomotor speed (Stroop, 1935, Golden, 1978). During this assessment, the participant was asked to read the colour of ink patches on the template (e.g., green, blue, red) as quickly as possible; the time limit was 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Stroop Interference Test

The Stroop Interference Test (SIT), as the third subtest, is used to measure response inhibition (Golden, 1978). The participants see words indicating colours (red, blue, green), each written in red, blue or green ink, incongruent to the colour indicated by the letters (e.g., the word 'red' written in blue ink). Participants have to inhibit uttering the words read and instead have to name the colour of the ink in which the incongruent colour names are printed. The time limit is 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Letter Fluency Test

The Letter Fluency Test (LFT) measures mental flexibility and semantic knowledge (Benton and Hamsher, 1976). In the LFT, participants were requested to utter as many words as possible, starting with a particular letter within one minute (response is speech motor output). LFT consists of three sub-tests, each using a different letter (i.g. S, M, T in German), tapping into the categories of high, medium and low frequency in the lexicon of the respective language (Senft, 2008). The total score as the sum of the correct, unique words of all sub-tests was recorded. The repetitive words count only once.

Categorial Fluency Test

In the Categorial Fluency Test (CFT), which is used to measure verbal learning and recall processes, participants are asked to name as many different words from the category "animals " as possible in one minute (Benton and Hamsher, 1976). The total of correctly named words (animals) was recorded.

Trail Making Test – Part A

The Trail Making Test (TMT) consists of A and B tasks, drawing straight lines connecting appropriate circles (Reitan, 1955). The TMT-A measures psychomotor speed. The rules for connecting circles labelled with numbers or letters differ between the two tasks: In the TMT-A, participants must connect given numbers in ascending order (i.e., 1-2-3-4), from 1 till 25. The time to complete the task is measured as a primary outcome, the number of failures or self-correction is also reported. TMT-A is an ideal measure of psychomotor speed.

Trail Making Test – Part B

The Trail Making Test – Part B (TMT-B) is the second task on the TMT with drawing straight lines connecting appropriate circles labelled with numbers and letters (Reitan, 1955). In the TMT-B, participants must connect given numbers and letters in alternating order (i.e., 1-A-2-B-3-C;). Thereby, the TMT-B taps executive and visual-perceptual functions, such as cognitive flexibility and selective attention abilities (Tombaugh, 2004). The time to complete the task is recorded as a primary outcome, the number of failures or self-correction is also reported.

Mini-Mental Status Examination

The Mini-Mental State Examination (MMSE) is a short screening questionnaire consisting of eleven tasks measuring five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The MMSE is a 30-point test, quick in the administration (5 minutes). It is widely used in clinical and research settings to assess general cognitive functioning and screen for pronounced cognitive decline. Higher scores indicate better cognition. The MMSE is applied as per the standard operating procedure of the original publication (Folstein et al., 1975).

2.4. Statistical Analyses

All statistical tests were performed using "IBM SPSS Statistics Software" for Windows, Version 22.0. The level of significance was set at $\alpha = 0.05$ (two-tailed). Normality of data was assessed using visual inspection of Quantile-Quantile plots (Q-Q plots) and Shapiro-Wilk tests. The significance of these results was used to decide whether parametric or non-parametric tests were to be performed subsequently. Continuous variables are expressed as mean, SD and range, while categorical variables are expressed as percentages and ordinal variables as medians. Age and education in years were characterised by mean and SDs, and gender was characterized as a binomial or nominal variable in percentages in relation to the whole sample. The descriptive statistical analysis was

performed to evaluate the number of study participants in both cohorts, in the manifest patient group (HD) and healthy controls (NC) and to assess their demographic characteristics. For all proportions calculated, 95% confidence intervals were also reported.

Spearman correlation coefficients (r) were used to evaluate the strength and direction of the linear relationships between two or more ordinal variables. The strength and direction of correlations between two or more continuous variables were calculated using Pearson correlation coefficients. In particular, Pearson's correlation coefficients were used to describe the strength and direction of the linear relationships between the test measures in the battery and the demographic variables of age and education.

The Pearson chi-square (χ_2) test was used for dichotomous variables. To evaluate differences among groups, independent-samples t-tests were applied. Effect sizes were reported in the form of Eta-Squared (η^2) and Cohen's d (as proposed by (Cohen, 1988). The Bonferroni correction for multiple comparisons was applied in between groups. Receiver Operating Characteristic (ROC) curves with area under the curve (AUC) and 95% Confidence Intervals (CIs) were calculated and used to compare the diagnostic accuracy of the neuropsychological tests included in the cognitive battery to assess cognitive impairment in HD. A one-way between-groups analysis of variance (ANOVA) was conducted to explore the impact of cognitive impairment in HD on the discriminative potential of each test included in the cognitive battery.

3. Results

3.1. Study Cohorts Description

3.1.1. Demographics and Clinical Characteristics

The main demographic and clinical characteristics of HD patients and healthy controls (NC) are displayed in Table 9. For the diagnosis of HD, the genetic test result with the number of CAG for both alleles of *htt* gene was recorded, giving the range between 39 to 57 CAG repeats length on the pathological allele and 12 to 28 on the physiological allele.

Further, the clinical characterization of the affected subsects was based on the main affected domains in HD. The motor phenotype was evaluated by the UHDRS-TMS (possible range 0–124) based on ratings on 15 standardized examination items (e.g., oculomotor function, dysarthria, chorea, dystonia, gait and postural stability).

The functional abilities were evaluated by the UHDRS-FIS, rating from 0 to 100 % based on 25 questions [yes/no], which evaluate the ability of a subject to carry out everyday activities independently. It is shown that the subjects' range of functional abilities varies from any impairment to severely impaired. Furthermore, the UHRDS-TFC score was used to evaluate the global functional ability based on five questions about occupation, finances, housework, activities of daily living and level of care, with a maximum score of 13 for no deficits, going down to 1 in our population in advanced stages of HD.

MMSE was performed in both groups to evaluate the general cognitive functioning and be applied for differentiation of the manifest patients with more and less pronounced cognitive impairment. A Mann-Whitney U-test revealed a significant difference in the global cognitive performance based on the MMSE total score between HD patients (M = 25.46, median = 26, SD = 4.39) and NC (M = 29.58, median = 30, SD = 0.76), U = 1684.00, z = −8.551, p < .001. Regarding all other demographic variables (i.e., gender, education, age), no significant a priori differences were found between HD patients and NC (all p's > .05, see Table 9).

Demographic and clinical characteristics of the HD (N = 106) and the NC (N = 100) group					
	HD (N = 106)		NC (N = 100)		
	M ± SD	Range	M ± SD	Range	p
Age (Y)	48.80 ± 13.39	20-79	48.47 ± 13.53	21-80	.970*
Education (Y)[1]	12.92 ± 2.30	8-20	13.41 ± 2.09	9-19	.054*
Gender (% male)	52.8		39.0		.064†
MMSE[2]	25.46 ± 4.39	9-30	29.58 ± 0.76	27-30	< .001*
UHDRS-FIS	18.37 ± 6.58	3-25			
UHDRS-TFC	8.63 ± 4.15	1-13			
UHDRS-TMS	31.42± 22.21	0-78			
CAG repeats[3]	17.86 ± 2.77	12-28 (normal allele)			
	44.22 ± 3.78	39-57 (mutant allele)			

Table 9: Demographic and clinical characteristic of HD patient and healthy control cohort
*Demographic and clinical characteristics of HD patient and healthy control cohort. Note: Y= years; MMSE = Mini-Mental State Examination; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-FIS = Functional Independence Scale; TFC = Total Functional Capacity; TMS = Total Motor Score; CAG = Cytosine-Adenine-Guanine. * Mann-Whitney U test for two independent samples was used to test for significance of group differences; † χ^2 -Test for independence (with Yates Continuity Correction) was used to test for significance of group differences; [1] analysis based on a sample size of N = 99 (NC); [2] analyses based on a sample size of N = 100 (HD) and N = 100 (NC); [3] analyses based on a sample size of N = 86 (normal allele) and N = 90 (mutant allele).*

3.1.2. Analyses of Disease Stages in Patient Cohort

The analysis of the functional ability of the manifest patient group based on UHDRS-TFC (more information in Table 5) was performed, allowing the distribution of the affected subjects into the respective disease stages I – V according to Fahn and Shoulson (Shoulson et al., 1989)., for more information see Table 5.

The evaluation showed the following distribution, referring to Stage I (TFC=11-13; N = 49), Stage II (TFC=7-10; N = 21), Stage III (TFC=3-6; N = 23) and Stage IV (TFC=1-2; N = 13), in detail displayed below in Table 10 .

Mean characteristics of HD patients in different disease stages according to TFC								
	Stage I (N = 49)		Stage II (N = 21)		Stage III (N = 23)		Stage IV (N = 13)	
	M ± SD	Range	M ± SD	Range	M ± SD	Range	M ± SD	Range
Age (Y)	46.57 ± 13.3	20-78	43.81± 13.24	21-67	56.35 ± 11.70	26-79	51.92 ± 11.65	38-78
Education (Y)	13.20 ± 2.63	9-20	12.95 ± 2.06	10-18	12.35 ± 2.06	8-17	12.85 ± 1.73	11-17
Gender (% male)	51.0		57.1		60.9		38.5	
MMSE1	27.53 ± 3.09	18-30	26.25 ± 2.97	20-30	22.27 ± 3.93	10-28	21.55 ± 6.07	9-30
UHDRS-FIS	23.78± 2.52	10-25	18.38 ± 3.52	13-23	12.00 ± 2.74	6-17	8.89 ± 6.37	3-25
UHDRS-TFC	12.35 ± 0.77	11-13	8.50 ± 1.16	7-10	4.43 ± 1.03	3-6	1.44 ± 0.53	1-2
UHDRS-TMS	15.35 ± 11.2	0-38	33.81 ± 15.0	8-63	53.76 ± 15.96	26-78	56.33 ± 14.98	23-73
CAG repeats								
Normal allele	18.15 ± 2.19	15-26	17.69 ± 2.65	15-24	17.57 ± 3.19	15-28	17.56 ± 4.30	12-28
Mutant allele	43.45 ± 2.94	40-52	47.25 ± 5.48	41-57	43.52 ± 3.11	39-55	44.56 ± 3.25	39-50

Table 10: Mean characteristics of HD patients in different disease stages according to TFC
Mean characteristics of HD patients in different disease stages according to TFC: Note. Y= years; MMSE = Mini-Mental State Examination; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-FIS = Functional Independence Scale; TFC = Total Functional Capacity; TMS = Total Motor Score;; CAG = Cytosine-Adenosine-Guanine

3.2. Results Interpretation in Clinical Practice

3.2.1. Diagnostic Accuracy in Detecting Cognitive Impairment

Sensitivity and Specificity to Distinct Cognitive Impairment between Manifest Patients and Healthy Controls

The diagnostic accuracy of the neuropsychological tests, namely SDMT, SWRT, SCNT, SIT, LFT, CFT, TMT-A and TMT-B, MMSE included in the cognitive battery was examined for its sensitivity and specificity to assess cognitive impairment in HD and to discriminate between HD patients (HD) and healthy controls (NC). Therefore, an independent-samples t-test (Welch's test) was conducted to compare the cognitive performance of the HD and NC population on each test included in the cognitive battery and to convey the significance of differences in the respective tests. There were significant differences in all test scores for HD and NC (all p's < .001; two-tailed) even after the Bonferroni correction for multiple comparisons with the HD patient group showing significantly worse cognitive performance than healthy matched controls. The magnitude of differences in the mean values was significant in each measure (for effect size Cohen's d see Table 11).

Between-group differences in the cognitive battery between HD (N = 106) and NC (N = 100)					
	HD (*N* = 106)	NC (*N* = 100)			
	M ± *SD*	*M* ± *SD*	*t*(df)	*p*	*d*
Letter Fluency (three letters) [1]	21.58 ± 13.50	39.39 ± 12.71	-9.15 (180)	< .001†	1.359
Stroop-Color Naming Test	44.05 ± 20.00	74.11 ± 12.71	-12.948 (179.3)	< .001†	1.794
Stroop-Word Reading Test	62.40 ± 28.76	102.70 ± 13.36	-13.014 (150.2)	< .001†	1.797
Stroop-Interference Test[2]	27.30 ± 13.30	42.83 ± 9.44	-9.326 (166.8)	< .001†	1.347
Symbol Digit Modalities Test	24.37 ± 16.07	47.35 ± 11.51	-11.851 (190.5)	< .001†	1.644
Categorical Fluency	13.79 ± 7.05	23.81 ± 5.43	-11.461 (196.2)	< .001†	1.592
Trail Making Test-A[3]	69.36 ± 53.84	25.44 ± 8.51	8.058 (103.9)	< .001†	-1.140
Trail Making Test-B[4]	144.54 ± 79.50	59.88 ± 29.46	9.762 (118.2)	< .001†	-1.412

Table 11: Between-group differences in the cognitive battery between HD patients and healthy controls
Between-group differences in the cognitive battery between HD patients and healthy controls Note. M = mean; SD = standard deviation; [1] analyses based on sample size of N = 83 (HD) and N = 99 (NC); [2] analyses based on sample size of N = 94 (HD); [3] analyses based on sample size of N = 100 (HD); [4] analyses based on sample size of N = 95 (HD); An independent-samples t-test (Welch's test) was used to test for significance of differences; † Significant after Bonferroni correction for multiple comparisons (p < .006); Classification and interpretation of effect size measure Cohen's d according to Cohen (1988): d = |0.2| (small effect); d = |0.5| (moderate effect); d = |0.8| (large effect); df = degrees of freedom.

Subsequently, the sensitivity and specificity of the cognitive battery to assess cognitive impairment in HD patients compared to normal cognitive functioning in healthy controls were assessed by applying the Receiver Operating Characteristic (ROC) analysis to examine the discriminative potential of each neuropsychological test included in the cognitive test battery to assess cognitive impairment in HD patients compared to NC group. The results are displayed in Table 12.

Sensitivity and specificity of the cognitive battery to assess cognitive impairment in the cognitive battery between HD and NC			
	AUC	95% CI	p
Letter Fluency (three letters)	.821	.758-.884	< .001
Stroop-Color Naming Test	.862*	.807-.917	< .001
Stroop-Word Reading Test	.844	.780-.908	< .001
Stroop-Interference Test	.809	.740-.877	< .001
Symbol Digit Modalities Test	.819	.752-.887	< .001
Categorical Fluency	.818	.754-.882	< .001
Trail Making Test-A	.831	.771-.891	< .001
Trail Making Test-B4	.813	.751-.875	< .001

Table 12: Sensitivity and specificity of the cognitive battery to assess cognitive impairment in HD patients compared to normal cognitive functioning in healthy controls
*Sensitivity and specificity of the cognitive battery to assess cognitive impairment in HD patients compared to normal cognitive functioning in healthy controls (NC, N = 100). Note. AUC = area under the curve (measures showing high discriminative potential with AUC > .80 are in bold; * neuropsychological test with the highest AUC); 95% CI = 95% confidence interval.*

As displayed above in Table 12, all examined tests showed high discriminative potential with AUC > 0.80 and p < .001. Based on the area under the curve (AUC) analyses the SCNT showed the highest potential to discriminate between the cognitive impairment between manifest HD patients and healthy controls (AUC = .862), followed by SWRT (AUC = .844), TMT-A (AUC = .831), LFT (AUC = .821), SDMT (AUC = .819), CFT (AUC = .818), TMT-B (AUC = .813) and SIT (AUC = .809) with the lowest discriminative potential. The respective graphical presentations of the diagnostic accuracy of the SDMT, all three Stroop Tests, Letter and Categorial Fluency and TMT-A and B by using ROC to disclose specificity and sensitivity in the differentiation of cognitive impairment between HD patients and healthy controls displayed in Figure 18.

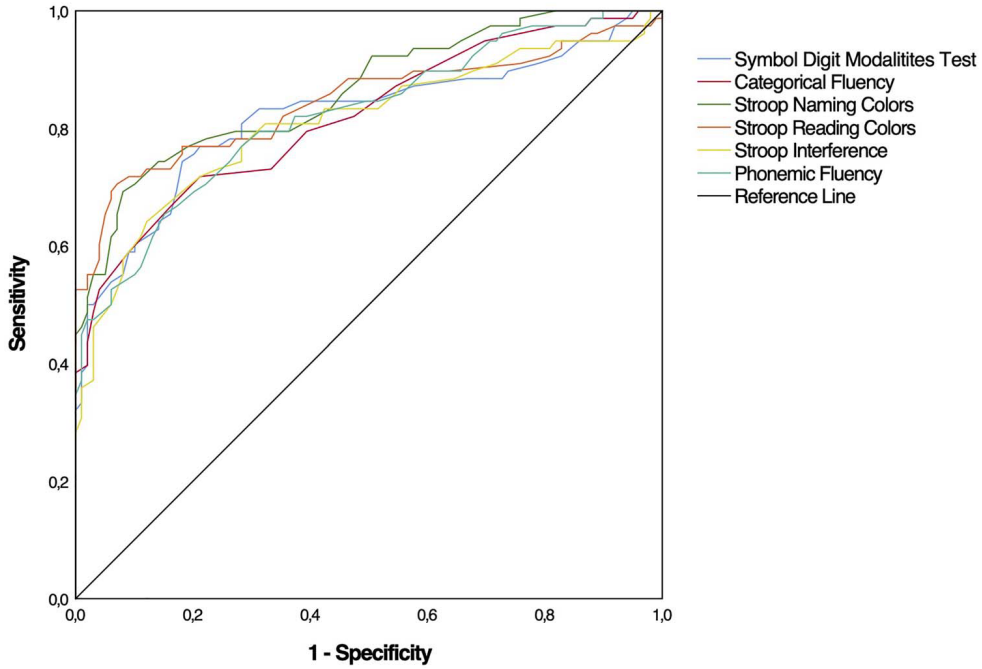


Figure 18: Diagnostic accuracy of the SDMT, Stroop tests and Fluency tests
Receiver-operating characteristic (ROC) discloses sensitivity and specificity of this cognitive battery to assess cognitive impairment and discriminate between HD patients (N = 106) and healthy controls (N = 100). Diagonal segments are produced by ties. y-axis = sensitivity; x-axis = 1 – specificity.

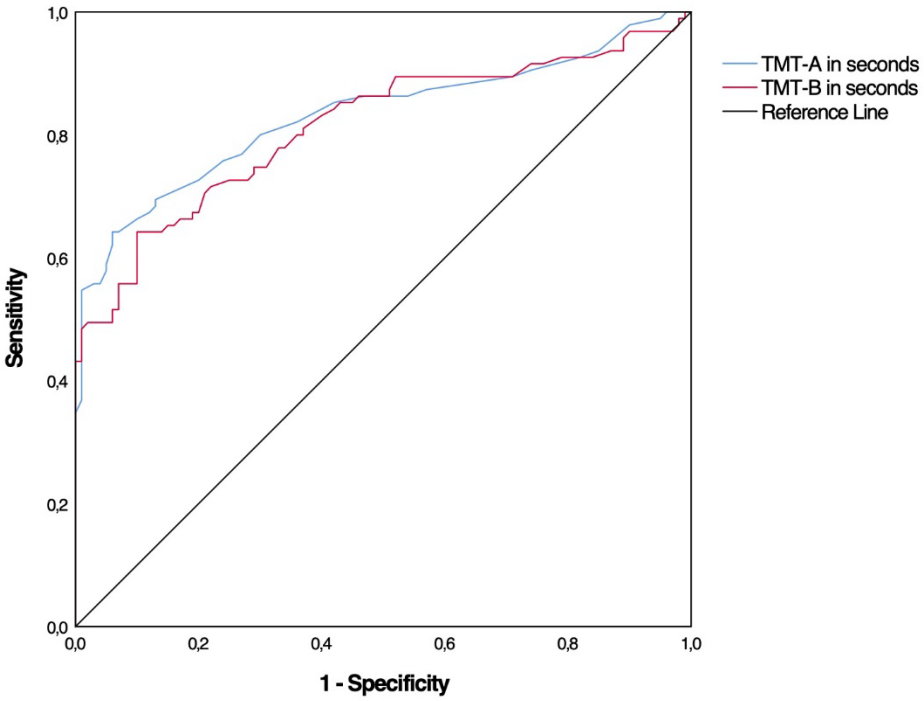


Figure 19: Diagnostic Accuracy of the Trail Making Tests.
Receiver-operating characteristic (ROC) discloses sensitivity and specificity of the TMT A and TMT-B to assess cognitive impairment and discriminate between HD patients (N = 106) and healthy controls (N = 100). Diagonal segments are produced by ties. y-axis = sensitivity; x-axis = 1 - specificity.

Sensitivity and Specificity to Distinct Cognitive Impairment between Patients with More and Less Cognitive Decline

In this study, for the purpose of further analyses of the manifest HD patient was divided into two subgroups, HD patients with a more pronounced cognitive deficit (HD-CD) and HD patients with a less pronounced cognitive deficit (HD-NC), by using the MMSE score as an instrument to assess the general cognitive function. The subgroup with HD patients with less pronounced cognitive impairment HD-NC showed MMSE ≥ 24, and the subgroup with HD with more pronounced cognitive deficit HD-CD showed MMSE <24. The MMSE was chosen to be used as a proxy to distinguish between HD patient groups with more and less cognitive deficits, as it is considered to be an established, conservative instrument to distinguish between moderate and severe cognitive impairments (Klempir et al., 2006, Mestre et al., 2018). The clinical and demographic characteristics of both subgroups, of the less (HD-NC) and more cognitively impaired (HD-CD), is displayed in Table 13.

Mean characteristics of less cognitively impaired HD-NC and more cognitively impaired HD-CD and healthy controls NC						
	HD-CD (N = 30)		HD-NC (N =70)		NC (N = 100)	
	M ± SD	Range	M ± SD	Range	M ± SD	Range
Age (Y) 1	54.13 ± 10.55	27-78	46.44 ± 14.18	20-79	48.66 ± 13.46	21-80
Education (Y) 1	12.63 ± 1.90	9-17	13.00 ± 2.47	8-20	13.41 ± 2.09	9-19
Gender (% male)	50.0		54.3		39.0	
MMSE	20.13 ± 3.67	9-23	27.74 ± 2.08	24-30	29.58 ± 0.76	27-30
UHDRS-FIS2	13.07 ± 5.66	3-25	21.20 ± 5.21	6-25		
UHDRS-TFC2	5.37 ± 3.46	1-13	10.27 ± 3.38	1-13		
UHDRS-TMS2	49.74 ± 18.71	17-78	23.00 ± 18.41	0-70		
CAG repeats2						
Normal allele	17.78 ± 3.80	12-28	17.87 ± 2.18	15-26		
Mutant allele	43.81 ± 2.75	39-55	44.47 ± 4.38	39-57		

Table 13: Mean characteristics of study groups
Mean characteristics of less cognitively impaired HD patients, more cognitively impaired (HD-CD) patients and healthy controls (HD-NC) group. Note. Y= years; MMSE = Mini-Mental State Examination; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-FIS = Functional Independence Scale; TFC = Total Functional Capacity; TMS = Total Motor Score; CAG = Cytosine-Adenine-Guanine; [1] analysis based on sample size of N = 99 (NC), [2]analyses based on sample size of N = 55 (HD-NC) and N = 27 (HD-CD).

Further in the study, the diagnostic accuracy of all tests included in the cognitive battery to discriminate between the cognitive deficit of HD patients with less and more pronounced cognitive impairment and healthy controls was evaluated. Therefore, one-way between-groups ANOVA was

applied to analyse the differences between the two patient subgroups and the control group in their cognitive performance on each neuropsychological test. The statistically significant differences (all $p < .001$) were recorded in all test scores between all three cohort groups. The results confirmed the expectation by showing that healthy controls performed significantly better than both HD patient subgroups and that HD-NC performed significantly better than HD-CD patients in all cognitive tests (NC > HD-NC > HD-CD), with all Games-Howell post-hoc tests $p < .001$. The obtained results of the ANOVA are displayed in Table 14; the core the corresponding descriptive statistics are shown in Table 14

Main effects of the one-way between-groups ANOVA performed on all neuropsychological tests included in the cognitive battery (F-values, preceded by corresponding degrees of freedom)				
	df1, df2	F	p	η^2
Letter Fluency (3 letters)	2, 177	56.09	< .001	.388
Stroop Colour Naming Test	2, 197	113.34	< .001	.535
Stroop Word Reading Test	2, 197	120.76	< .001	.551
Stroop Interference Test	2, 187	71.74	< .001	.434
Symbol Digit Modalities Test	2, 197	101.80	< .001	.508
Categorical Fluency	2,197	93.98	< .001	.488
Trail Making Test-A	2, 193	70.66	< .001	.423
Trail Making Test-B	2, 189	93.41	< .001	.497

Table 14: Main effects of the one-way between-groups ANOVA performed on all neuropsychological tests included in the cognitive battery
Classification and interpretation of effect size measure η2 according Cohen (1988) (η2 = .01 (small effect); η2 = .06 (moderate effect); η2 = .14 (large effect); df = degrees of freedom.

Between-group differences in the cognitive battery in patients with less cognitively impaired HD-NC (N = 70) and more cognitively impaired HD-CD (N = 30) and controls NC (N = 100) groups			
	HD-CD (N = 30)	HD-NC (N = 70)	NC (N = 100)
	M ± SD	M ± SD	M ± SD
Letter Fluency (3 letters)	10.95 ± 8.48	25.10 ± 13.22	39.39 ± 12.71
Stroop Colour Naming Test	29.93 ± 16.85	51.54 ± 17.43	74.11 ± 12.71
Stroop Word Reading Test	42.23 ± 17.34	72.94 ± 27.37	102.70 ± 13.36
Stroop Interference Test	15.43 ± 10.08	31.66 ± 11.87	42.83 ± 9.44
Symbol Digit Modalities Test	11.80 ± 8.06	30.53 ± 15.46	47.35 ± 11.51
Categorical Fluency	8.63 ± 3.61	16.24 ± 6.67	23.81 ± 5.43
Trail Making Test-A	108.88 ± 63.94	53.23 ± 36.85	25.44 ± 8.51
Trail Making Test-B	213.88 ± 42.46	120.72 ± 75.29	59.88 ± 29.46

Table 15: Between-group differences in the cognitive battery
Comparison of HD patients with less and more pronounced cognitive impairments and healthy controls. Note. M = mean; SD = standard deviation; 1 analysis based on sample size of N = 99 (NC), N = 60 (HD-NC), N = 21 (HD-CD); 2 analyses based on sample size of N = 67 (HD-NC), N = 23 (HD-CD); 3 analyses based on sample size of N = 26 (HD-CD); 4 analyses based on sample size of N = 68 (HD-NC), N = 24 (HD-CD).

Subsequently, ROC analysis was performed to investigate the sensitivity and specificity of each neuropsychological test to discriminate between two patients' subgroups, HD-NC and HD-CD patients, based on their cognitive performance. As displayed in Table 16, all tests showed high discriminative potential with all AUC > 0.80 and all p < .001. based on AUC analyses, the highest discriminative potential was detected for the Stroop Color Naming Test (AUC = .899) to discriminate between the patients with less and more cognitive impairments, followed by Stroop Interference Test (AUC = .894), SDMT (AUC = .892), Stroop Word Reading Test (AUC = .887), Categorical Fluency Test (AUC = .863), Letter Fluency Test (AUC = .848), TMT-B (AUC = .835) and TMT-A (AUC = .833) with the lowest discriminative potential.

Sensitivity and specificity of the cognitive battery to discriminate between HD patients with more (HD-CD, N = 30) and less cognitive impairments (HD-NC, N = 70)			
	AUC	95% CI	p
Letter Fluency (3 letters)	.848	.749-.947	< .001
Stroop Colour Naming Test	.899*	.810-.988	< .001
Stroop Word Reading Test	.887	.803-.970	< .001
Stroop Interference Test	.894	.791-.997	< .001
Symbol Digit Modalities Test	.892	.808-.976	< .001
Categorical Fluency	.863	.781-.945	< .001
Trail Making Test-A	.833	.748-.917	< .001
Trail Making Test-B	.835	.754-.915	< .001

Table 16: Sensitivity and specificity of the cognitive battery to discriminate between HD patients with less and more cognitive impairments

*Note. AUC = area under the curve (measures showing high discriminative potential with AUC > .80 are in bold; * neuropsychological test with the highest AUC); 95% CI = 95% confidence interval.*

The respective graphical presentations of the diagnostic accuracy of the SDMT, all three Stroop tests, Letter and Categorial Fluency and TMT-A and B by using ROC to disclose specificity and sensitivity in the differentiation of cognitive performance between HD patients with less and more cognitive impairments are displayed in Figure 20 and Figure 21.

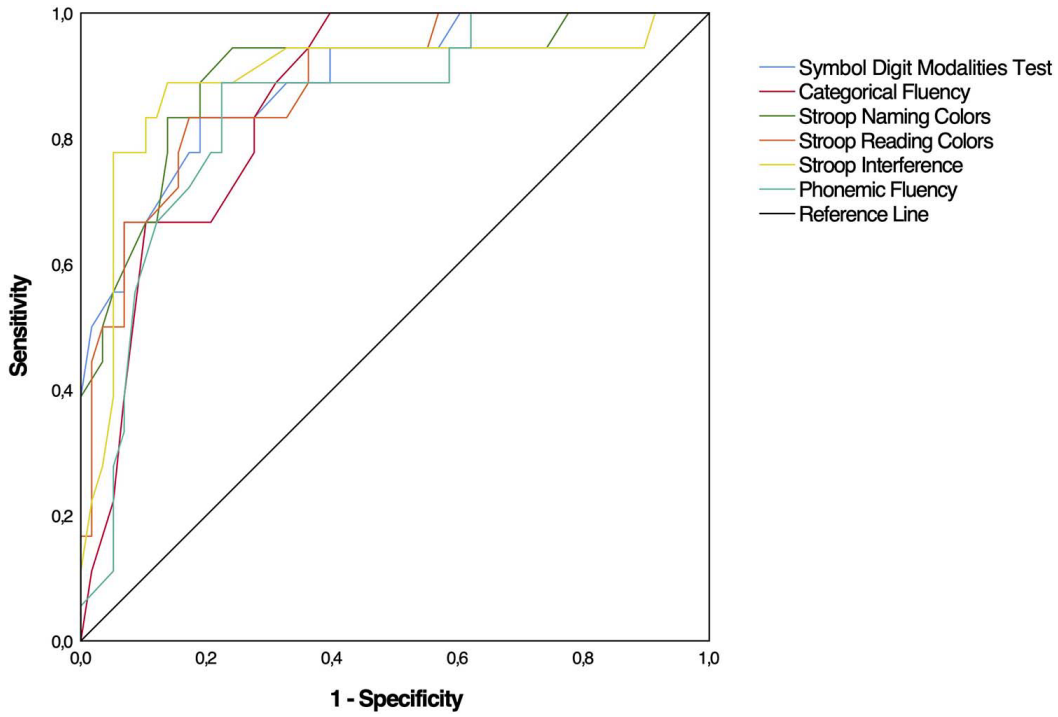


Figure 20: Diagnostic accuracy of the SDMT, Stroop and Fluency Tests -
Receiver-operating characteristic (ROC) discloses sensitivity and specificity of this cognitive battery to assess cognitive impairment and discriminate between HD patients with less (HD-NC, N = 70) and more pronounced cognitive impairment (HD-CD, N = 30). Diagonal segments are produced by ties. y-axis = sensitivity; x-axis = 1 – specificity.

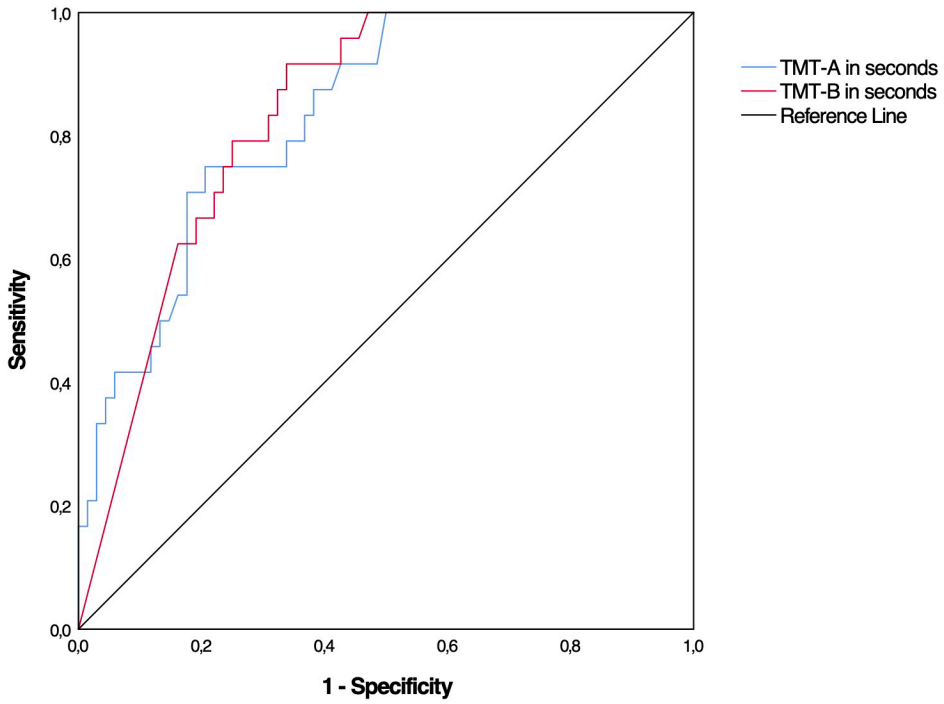


Figure 21: Diagnostic accuracy of the Trail Making Test A and B
Receiver-operating characteristic (ROC) discloses sensitivity and specificity of TMT A and B to assess cognitive impairment and discriminate between HD patients with less (HD-NC, N = 70) and more pronounced cognitive impairment (HD-CD, N = 30). Diagonal segments are produced by ties. y-axis = sensitivity; x-axis = 1 – specificity.

3.2.2. Effect of Individual Factors on Cognitive Performance and Relationship of Cognitive, Motor and Functional Status

Effects of Disease Progression

In this study, the individual factors were examined using partial correlation analysis to closely examine the effects of the individual factors on the neuropsychological tests and cognitive performance and the relationship between cognitive performance, motor impairment and functional decline on the other hand. All results, including correlation coefficients r- and p-values, are shown in Table 17 below.

Pairwise partial correlations between the respective neuropsychological tests of the cognitive battery (shown in rows) and clinical variables (shown in columns) by considering and controlling for the influence of the tertiary variables for disease duration and age

Clinical variables	UHDRS TMS	UHDRS TO	UHDRS TB	UHDRS TR	UHDRS TD	UHRDS TCH	TFC	FIS	DBS
MMSE	**-.575*** **	**-.512*** **	**-.592*** **	-.318*	-.425**	-.420**	**.575*** **	**.603*** **	-.227
VFT	**-.589*** **	**-.513*** **	**-.621*** **	-.298*	-.345*	**-.521*** **	**.501*** **	.486***	-.488***
SCNT	**-.666*** **	**-.593*** **	**-.693*** **	-.464***	-.447**	-.494***	**.572*** **	**.640*** **	**-.516*** **
SWRT	**-.619*** **	**-.560*** **	**-.647*** **	-.363**	-.437**	-.442**	**.609*** **	**.566*** **	**-.556*** **
SIT	**-.648*** **	**-.586*** **	**-.673*** **	-.400**	-.448**	-.473***	.476***	**.617*** **	-.325*
SDMT	**-.660*** **	**-.638*** **	**-.674*** **	-.411**	-.387**	**-.521*** **	**.627*** **	**.615*** **	**-.596*** **
CFT	-.472***	-.391**	**-.500*** **	-.184	-.304*	-.426**	.427**	.461**	-.315*
TMT-A	**.573*** **	**.613*** **	**.589*** **	.392**	.356**	.337*	**-.512*** **	**-.569*** **	.331*
TMT-B	**.550*** **	**.556*** **	**.616*** **	.384**	.275*	.338*	**-.559*** **	**-.615*** **	.422**

Table 17: Pairwise partial correlations between the respective neuropsychological tests of the cognitive battery and clinical variables.

*Note: CAG = Cytosine-Adenine-Guanine, DBS = Disease Burden Score, DBS=(CAG_n-35.5) x age; MMSE = Mini-Mental State Examination; VFT = Verbal Fluency Test; SCNT = Stroop Color Naming Test; SWRT = Stroop Word Reading Test; SIT = Stroop Interference Test, Interference; SDMT = Symbol Digit Modalities test; CFT = Categorial Fluency Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; UHDRS = Unified Huntington's Disease Rating Scale; UHDRS-FIS = functional independence scale (possible range: 0–100); TFC = Total Functional Capacity (possible range: 1–13). UHDRS-TMS = UHDRS-Total Motor Score (possible range: 0–124); UHDRS-TO = UHDRS-Total Oculomotor; UHDRS-TB = UHDRS-Total Bradykinesia; UHDRS-TR = UHDRS-Total Rigidity; UHDRS-TD = UHDRS-Total Dystonia; UHDRS-TCH = UHDRS-Total Chorea; analyses based on N = 55 observations of HD patient group; Interpretation of effect size according to Cohen(1988), r < 0.1 may be interpreted as no effect; 0.1 ≤ r < 0.3 indicates a small effect size; 0.3 ≤ r < 0.5 refers to a moderate effect size; r ≥ 0.5 is equivalent to a strong effect size; correlations coefficients equivalent to a strong effect size are written in bold; * p < .05; ** p < .01; *** p < .001.*

The results indicated that the cognitive deficits detected in almost all neuropsychological tests (apart from the MMSE score) progressed with the duration of the disease, suggesting the SDMT and SCNT as the most significant ones. Moreover, results indicate that the Disease Burden Score (DBS), an indicator for the pathological burden of a patient caused by lifetime exposure to mutant

huntingtin (i.e., disease burden), was significantly correlated with the cognitive performance on nearly all neuropsychological tests (except MMSE with r = −.227, p = .102) regardless of disease duration and current age: SDMT (r = −.596, p < .001), Stroop Word Reading Test (r = −.556, p < .001), Stroop Color Naming Test (r = −.516, p < .001), Letter Fluency Test (r = −.488, p < .001), TMT-B (r = .422, p < .01), TMT-A (r = .331, p < .05), Stroop Interference Test (r = −.325, p < .05) and Categorical Fluency Test (r = −.315, p < .05). An overview of all coefficients is presented in Table 17.

Effect of Motor Functions

The closer analyses concerning the relation of motor and cognitive status, the results showed that the severity of overall motor impairments recorded as the total motor score of the UHDRS-TMS.is r ranging from −.472 to −.666; all p's < .001 correlates with the cognitive performance on nearly all cognitive test, except Categorical Fluency Test. The UHDRS-TMS comprises 15 items and has a maximum score of 124. The different items of the UHDRS-TMS are organized in the following categories to build the sub-scores on the respective motor subdomains such as oculomotor function represented by the UHDRS-TO = UHDRS-Total Oculomotor; slowness as bradykinesia represented by the UHDRS-TB = UHDRS-Total Bradykinesia; parkinsonian or rigidity refers to the UHDRS-TR = UHDRS-Total Rigidity, followed by the UHDRS-TD = UHDRS-Total Dystonia and involuntary choreatic movements represented such as the UHDRS-TCH = UHDRS-Total Chorea.

The results on the effect of total motor function and motor sub-scores on cognitive performance are displayed in Table 17. The following results on the different sub-scores were detected as follows: Bradykinesia (UHDRS-TB; r ranging from −.500 to −.693; all p's < .001) and oculomotor impairment (UHDRS-TO; r ranging from −.391 to −.638, all p's < .001, except categorical fluency with p < .01), were significantly correlated with performance on all cognitive tests. Dystonia (UHDRS-TD; r ranging from .275 to −.448, all p's at least <.05) and chorea (UHDRS-CH; r ranging from −.337 to −.521; all p's at least <.05) and rigidity (UHDRS-TR; r ranging from −.184 to −.464; all p's < .05 except categorical fluency with p = .187) were as well significantly correlated with performance on all cognitive tests. Hence, the degrees of rigidity (UHDRS-TR) and dystonia (UHDRS-TD) were less strongly related to cognitive performance. Thus, the severity of motor impairment in different domains (UHDRS: TMS, oculomotor, bradykinesia, rigidity, dystonia and chorea) was closely associated with the severity of cognitive deficits.

Effect of Functional Status

Regarding the link between functional and cognitive status, correlation analysis is presented in Table 17 suggested that TFC and FIS correlated with performance on all neuropsychological tests

with moderate to large correlation coefficients. TFC with r ranging from .427 to .627 (all p's < .001 except categorical fluency with p < .01) and as well FIS with r ranging from .461 to .640 (all p's < .001 except categorical fluency with p < .01) were significantly correlated. Thus, the severity of deficits in all cognitive functions represented with poorer performance in neuropsychological tests was strongly associated with functional disabilities.

4. Discussion

The main objective of the present study was to examine the diagnostic accuracy of the Enroll-HD cognitive battery consisting of the Symbol Digit Modalities Test, Stroop Color Naming Test, Stroop Word Reading Test, Stroop Interference Test, Letter and Categorical Fluency Test, Trail Making Test A and B and MMSE, to assess cognitive impairment and to distinguish between HD patients and healthy controls and between HD patients with more and less pronounced cognitive impairment. Moreover, it aimed to explore the relationship between cognitive, motor and functional status and the effect of disease burden on cognition.

4.1. Sensitivity and Specificity of the Cognitive Battery to Assess Cognitive Impairment in HD

This study revealed that all cognitive tests included in the examined cognitive battery are sufficiently sensitive and specific to capture cognitive deficits in HD patients compared to healthy controls, as displayed in Table 11and Table 12. The following tests placed in descending order were found to have the highest discriminatory properties to distinguish between healthy controls and HD patients: Stroop Color Naming Test, Stroop Word Reading Test, TMT-A, Letter Fluency Test, SDMT, Categorical Fluency Test, TMT-B and Stroop Interference Test. All examined neuropsychological tests are suitable for identifying early cognitive or subtle impairments. Paulsen et al. referred to the SWRT as one of the strongest cognitive predictors for the cognitive deficits prior to the onset of motor diagnosis (Paulsen et al., 2014a). The SWRT consistently showed strong discriminative properties to detect a cognitive deficit in this study.

The same applies to the SDMT as this test has been a highly sensitive and consistent task for tracking decline in HD. Several studies identified SDMT as a key instrument for identifying early cognitive impairment in premanifest subjects and tracking the progression of cognitive decline in the longitudinal matter (Paulsen and Long, 2014). In this study, we examined the group of patients

in the early stages of HD. We confirmed the previously reported finding by Paulsen et al. that identified SDMT to be very sensitive in identifying the cognitive deficit in the early stages of HD. As the SDMT measures psychomotor speed, we could consider this cognitive domain to be an important and early predictor of the cognitive decline in premanifest and early manifest with HD affected individuals (Stout et al., 2011, Stout et al., 2012, Paulsen et al., 2014a, Larsen et al., 2015).

The CFT appears to be more sensitive in detecting early cognitive impairments than the LFT. However, the LFT places greater demand on the executive function, as this task requires retrieving the words from a phonetic (letter) category. In this approach, the automatic activation of semantically related words needs to be suppressed, and novel retrieval strategies need to be applied that require quick decision-making and rely greatly on obtained education of a person (Feigin et al., 1995, Katzev et al., 2013, Friesen et al., 2015). In contrast, the CFT applies more to the automated process and uses the existing semantic links between the words retrieved during the assessment (Shao et al., 2014). Although there is no major cognitive deficit in the semantic memory in HD (Snowden, 2017, Nikolai et al., 2018), overall, the verbal fluency tasks present difficulties for the affected HD individual in terms of time needed for the participant to respond to the task and the impaired speech tempo to carry out the correct answer as the motor output representing the impairments in the psychomotor speed (Lemiere et al., 2002, Tabrizi et al., 2011, Tabrizi et al., 2012, Paulsen et al., 2014a, Larsen et al., 2015).

It is assumed that in the early stages of HD, the affected patients can compensate for the cognitive deficits due to the good maintain cognitive reserve (Tucker-Drob et al., 2009, Gonzalez-Burgos et al., 2020) and well-preserved functions of the frontal lobes (Stout et al., 2011, Giralt et al., 2012). In the further course of the HD, the striatum and the frontostriatal network degeneration subsequently leads to depletion of cognitive reserves (Domínguez D et al., 2017), in particular, to executive control dysfunction, leading to significant deficits in assessments demand mostly on executive functions, such as TMT-A, TMT-B, Letter Fluency Test and Stroop Interference Test (Dumas et al., 2013a, Paulsen et al., 2017, Snowden, 2017), an overview of single tests and their properties to distinguish the cognitive deficit is showed in Table 15 and Table 16.

4.2. Sensitivity and Specificity of the Cognitive Battery to Differentiate More and Less Pronounced Cognitive Impairments in HD

The MMSE plays an important role in clinical practice as a screening tool for assessing cognitive decline (Ringkøbing et al., 2020). It also remains an important part of everyday clinic due to its time efficiency and simple administration. However, a more precise assessment of functional and cognitive abilities is required to warrant a diagnosis of dementia. Although the MMSE is a useful tool as it provides basic information on the ability of the patient to participate in further cognitive testing (Mestre et al., 2018; Peavy et al., 2010), there is a need to implement further easy in administration neuropsychological tools to assess cognitive impairments and provide quick sensitive and specific screening tool to detect the cognitive impairment for HD.

The findings showed that the MMSE contrasts the neuropsychological tests SDMT; SWRT; SCNT; SIT; TMT-A and B, LFT; CFT, does not correlate with the DBS and therefore, it is not a suitable indicator to detect progression of HD (Table 17). Not surprisingly, the Stroop tests and SDMT have the highest correlation with the DBS, as these instruments are already known to monitor the disease progression continuously (Lemiere et al., 2002, Lemiere et al., 2004, Paulsen et al., 2014a).

The results from ANOVA analysis showed that every test included in the Enroll-HD cognitive battery has a very high diagnostic accuracy for differencing cognitive impairment in HD and is specific to capture and differentiate the level of the cognitive deficits in HD patients with more and less pronounced cognitive impairments (see Figure 20, Figure 21 and Table 16. Notably, the results confirmed, the differences between the two patient subgroups with more (HD-CD) and less pronounced cognitive deficits(HD-NC) were highly significant, giving high levels of classification accuracy based on sensitivity and specificity in ROC space (as shown in Table 16). Looking closely at the given results, the highest discriminative properties to distinguish between those patient subgroups were found in the following tests in descending order: SCNT, SIT, SDMT, SWRT, CFT, LFT, TMT-B and TMT-A (see Table 16).

Overall, it appears that more complex tests in the administration or a combination of several tests are needed to assess cognitive performance and to distinguish between HD patients in different disease stages with more and less pronounced cognitive impairment, as referred to in Table 16. In this way, the MMSE may be used as an initial screening to provide quick information on the global cognitive functioning and then more precise neuropsychological tests to assess the cognitive domains specific for HD.

4.3. Relation between Cognitive Performance, Motor Impairment, Functional Decline and Disease Burden

4.3.1. Cognitive Performance and Motor Impairments

After excluding the variables for age and disease duration, the partial correlation analysis revealed the relationship between motor function assessed by the Total Motor Score (TMS) assessment of the UHRDS and cognitive deficits using the cognitive battery. The results from the clinical motor examination of the UHDRS are building the sub scores for the oculomotor, bradykinesia, rigidity, chorea and dystonia deficits. As indicated in Table 17, pairwise partial correlations between the respective neuropsychological tests of the cognitive battery, clinical variables and motor domain subscores showed that the cognitive deficits were most significantly correlated with the severity level of bradykinesia as with oculomotor deficits and chorea. In contrast, the levels of dystonia and rigidity were less strongly associated with cognitive deficits. The rationale behind this is that the basal ganglia circuits are the brain regions involved in motor and cognitive performance and are predominantly early affected by the neurodegenerative process in HD (Bonelli & Cummings, 2007; Georgiou-Karistianis et al., 2013; Rüb et al., 2015). The cortical loops serve to coordinate motor and cognitive function integrated into the basal ganglia (Alexander, 1986; Klempíř, Klempířová, Štochl, Špačková, & Roth, 2009; Ross, Pantelyat, Kogan, & Brandt, 2014).

Moreover, the study results confirm are consistent with findings from the clinical practice demonstrating that motor impairment, especially bradykinesia, is an important factor predicting and contributing to the decline in cognitive performance of HD (Baake et al., 2017; Long et al., 2014; van Vugt et al., 2004).

4.3.2. Cognitive Performance and Functional Abilities

Additionally, the analysis to assess the association between cognition and functional abilities in patients with more (HD-CD) and less pronounced cognitive impairments (HD-NC) was performed, and the results confirmed that the cognitive performance of HD patients on all neuropsychological tests was significantly correlated to their functional abilities (see Table 17). The findings confirmed that the pronounced cognitive impairment was associated with a higher loss of functional abilities, which is well known in affected HD individuals and resulting in difficulties in everyday functioning (Beglinger et al., 2010b). This is in line with multiple studies showing the impact of the cognitive deficit on functional abilities and everyday life functioning (Duff et al., 2010a). It also corresponds with the reports of the relatives, partners, caregivers and other family members of HD patients that

cognition is one of the most decisive factors for everyday life abilities. The first difficulty disrupting the activities of daily living occur already with the very early subtitle changes in cognition (Beglinger et al., 2010b, Beglinger et al., 2012).

In this respect, the study results support the frequently used criteria for the diagnosis of dementia in HD patients, according to which the presence of dementia is determined by significant functional deficits leading to the following scores UHDRS-TFC > Stage II and UHDRS-FIS < 80% (Peavy et al., 2010). However, more studies are needed to implement and define the definition for HD dementia more precisely.

In summary, the present results provided evidence that although HD is classically considered to be a motor disorder, cognitive decline already occurs in the early stages of the disease (Paulsen, 2011; Stout et al., 2011) and are significantly associated with the deterioration of the patients' functional abilities (Beglinger et al., 2012; Paulsen et al., 2014; Ready et al., 2008; Snowden, 2017). This early detectable cognitive decline reflects the impairment and loss of other neuronal populations, such as cortical and hippocampal neurons, by the presence of mutant *htt* and its toxic effect, which increase with the length of the polyglutamine chain (Nopoulos et al., 2010, Giralt et al., 2012, Paulsen et al., 2014a). There are interactions among striatal, cortical and hippocampal systems, and the final cognitive outcome depends on compensatory and interactions mechanisms within those systems (Giralt et al., 2012). Consequently, the impairments in cognitive functions lead to the deterioration of motor performance and functional capacity.

4.3.3. Cognitive Performance and Disease Burden

The present study results confirmed that disease burden displayed as the Disease Burden Score (DBS) score was associated with cognitive performance regardless of age and disease duration, but not to the same extent for each test included in the cognitive battery (see Table 17). More precisely, the DBS established as a product of CAG length and age (see section 6.3) was significantly correlated with the performance on the following cognitive tests in descending order: SDMT, SWRT, SCNT, LFT, TMT-B, TMT-A, SIT and CFT. Thus, the higher DBS was associated with poorer performance on the neuropsychological tests. This is consistent with findings from previous studies indicating that CAG length, as an indicator for genetic load, influences disease progression (Andrew et al., 1993) and cognitive performance (Paulsen et al., 2013, Baake et al., 2017). To some extent, is the DBS an index conveying the toxicity exposure to the mHTT protein (Harrison et al., 2015, Pini et al., 2020) and highlighting the close relationship between corticostriatal degeneration process and cognition performance in HD.

Moreover, the study results showed that the MMSE is the only neuropsychological test that is not significantly correlated to the DBS (see Table 17: Pairwise partial correlations between the respective neuropsychological tests of the cognitive battery and clinical variables.). Thus, it can emphasize that the MMSE as a screening tool for assessing global cognitive functioning does not reflect well the cognitive deterioration process in HD. This finding is in accordance with previous studies, which demonstrate the MMSE is not sufficiently specific and sensitive to assess and continuously monitor the cognitive decline in the course of the disease in HD patients (Peavy et al., 2010, Bezdicek et al., 2013, Toh et al., 2014, Mestre et al., 2018, Ringkøbing et al., 2020).

4.4. Limitations

One of the limitations of the present study is the complexity of assessing executive functions, including multifaceted tasks such as planning, controlling and maintaining attention, organising, abstract thinking, problem-solving, control of actions, cognitive flexibility, and set-shifting (Lezak, Howieson, Bigler, & Tranel, 2012). Unfortunately, no single measure of executive function is available as the multitude of different cognitive abilities are considered part of executive functions (Homack & Riccio, 2004). Therefore, the neuropsychological test battery includes different tests to assess the different subdomains of executive function and psychomotor speed. However, it can be argued that not all parts of executive functions have been examined, as the investigated cognitive battery does not explicitly examine memory, planning and visuospatial function. Therefore, some additional tests may be m needed to apply to ass all cognitive domains.

This cognitive battery includes the MMSE as a screening tool to assess the global cognitive impairment in HD patients. However, there is no sufficient evidence if MMSE offers enough sensitivity and specificity to discriminate the global cognitive impairment in HD from normal cognitive functioning or mild cognitive impairment (MCI) (Bezdicek et al., 2013). It is desirable to detect mild cognitive deficits in the early and pre-symptomatic stages of HD and discriminate between HD patients with pronounced and less pronounced cognitive impairment. This will be a subject of future studies. However, the sample sizes were relatively small, and thus, the results are of limited generalizability, but all results were significant using rather conservative statistical thresholds. Therefore, future studies should examine larger samples to ensure the generalizability of the results.

5. Conclusions

In summary, the present results provide further evidence that although HD is classically considered to be a motor disorder, cognitive decline already occurs in the early stages of the disease (Paulsen, 2011; Stout et al., 2011) and are highly associated with the deterioration of the patients' functional abilities (Beglinger et al., 2012; Paulsen et al., 2014; Ready et al., 2008; Snowden, 2017). However, there is solid evidence that subtle cognitive deficits in the following domains: attention, working memory, processing speed, psychomotor functions, episodic memory, emotion processing, perception and executive functions precede the emergence of diagnostic motor signs decades prior to the onset (Kirkwood et al., 2000, Paulsen et al., 2008, Snowden, 2017). The cognitive decline in HD is progressive and associated with functional impairment (Snowden, 2017); therefore, assessing cognition is crucial for tracking disease progression (Stout et al., 2012, Tabrizi et al., 2012).

Overall, it is to assume that neuropsychological tests, including the tested cognitive battery SDMT; SWRT, SCNT, SIT, TMT-A and B, LFT, CFT, offer sufficient sensitivity and specificity to identify continuously monitor the cognitive performance and the disease progression. For these purposes is essential to use appropriate, sensitive tests suitable for repeated application in the longitudinal matter. In contrast, it is important to emphasize the non-specificity of the MMSE versus the specificity of the tested cognitive battery for assessing characteristic cognitive deficits in HD patients. However, MMSE will still have its place as a screening tool in clinical practice. Specific cognitive deficits in the early stages of HD include psychomotor slowing and disruption of executive functions involving the deficits in automated activities, such as speech, reading and coding (Snowden et al., 2001, Thompson et al., 2012, Snowden, 2017), that the investigated cognitive battery can appropriately assess. Overall, this cognitive battery's simpler and quick administration seems to be sufficient and enough sensitive in assessing cognitive deficits in HD.

III. Establishing Multilingual Normative Data for the Evaluation of Cognitive Performance in Huntington disease with a Normative Calculator (Study II)

1. Study Aims and Hypothesis

The identification and monitoring of cognitive impairments in HD are of great importance, as it is one of the earliest signs of disease manifestation. Several observational studies have highlighted the importance of monitoring the longitudinally cognitive decline at the very early stages of the disease process (clinically called a premanifest HD) in order to track the progression of the disease and provide sufficient support and care od affected individuals (Tabrizi et al., 2013b, Paulsen et al., 2014a, Julayanont et al., 2020).

Therefore, objective neuropsychological assessments are needed to evaluate the key domains of cognitive functioning and determine appropriate diagnosis, aetiology and severity of the cognitive decline (Sachdev et al., 2014). At the same time, it is important to apply the appropriate norm data when evaluating the neuropsychological assessment to define the disease-associated decline and differentiate the cofounding factors such as age, gender, language and cultural background, and education level that can influence cognitive performance.

In this study, the Enroll-HD cognitive battery (Sathe et al., 2021), as one of the most commonly used batteries in the field of HD, was investigated. This cognitive battery originates from the United Huntington Disease Rating Scale (UHDRS) introduced to the clinical and research practice by Huntington Study Group (Huntington Study Group, 1996). The following tests are included: Symbol Digit Modalities Test (SDMT), Stroop Tests consisting of the Stroop Word Reading Test (SWRT), Stroop Colour Naming Test (SCNT) and Stroop Interference Test (SIT), Trail Making Test – Part A and Part B (TMT-A and TMT-B), Letter Fluency Test (LFT) and Category Fluency Test (CFT) and Mini-mental Status Examination (MMSE). The several tests of this cognitive battery underwent further comprehensive development. They differed in essential ways from the original test version and mode of application described in the respective foundational publications. E.g. Stroop described initially using the five colours red, blue, green, brown and purple and monitored time to test

completion as the raw score (Stroop, 1935). Golden evaluated different variations of Stroop tests and changed the matrix of all three tests SWRT, SCNT, SIT, to the current standardized version, involving three instead of five colours, with 100 items (words/colours) printed per card and stopping probands after 45 seconds, using the number of correct answers as the raw score (Golden, 1978). No normative data for this particular mode of application have been derived from the original publication of the respective tests; only scattered normative data, restricted to a few languages, are published (Scarpina and Tagini, 2017).

Further, the Unified Huntington's Disease Rating Scale (UDHRS), a clinical scale developed by the Huntington Study Group, with a final version introduced in 1996, to assess four main domains in HD: motor function, behavioural abnormalities, functional capacity and cognitive function, is widely used in research and clinical practice (Huntington Study Group, 1996). Stout et al. conducted a structured meta-analysis of cognitive measures in HD, including the cognitive battery of the UHDS to identify the most appropriate ones for longitudinal assessments, informing the selection of the cognitive battery for the observational cohort study Enroll-HD (Landwehrmeyer et al., 2017). The same or similar cognitive assessments are used in other primary neurodegenerative conditions, e.g. PD (Jalakas et al., 2019, Statucka and Cohn, 2019, Sanchez-Luengos et al., 2021), FTD (Plutino et al., 2020) and PSP (Plutino et al., 2020), as well as in secondary neurodegenerative conditions like MS (Chiaravalloti and Deluca, 2008, Langdon et al., 2012, Kalb et al., 2018, Middleton et al., 2020).

In addition, when evaluating cognitive deficits, it is important to consider the impact of confounding factors, such as age, gender, language and cultural background and education level, that can influence cognitive performance (Baños, 2018). It is important to capture these confounding factors to isolate the effects of disease progression. Understanding age-related biological changes in cognition are important given the increasing number of older people and the importance of one's ability to maintain functional independence (Murman, 2015). The education level may vary across the population and influence the performance in cognitive testing and needs to be considered in the evaluation (Lam et al., 2013). Overall, it is important to address cultural and language biases on cognitive testing (Statucka and Cohn, 2019). It needs to establish the strategies taking the cofounding factors into account.

1.1. Primary Aims

The study aimed to evaluate the cognitive decline and dissect the disease-associated decline in cognitive performance of HD by minimizing the impact of confounding factors, consisting of age, language, gender and educational background at a single subject level.

For this purpose, this study aimed to develop a normative calculator to convert raw test scores of the cognitive battery consisting of the SDMT, SWRT, SCNT, SIT, TMT-A and TMT B, CFT and LFT to the regression-based *z*-scores based on healthy control samples. The second step aimed to apply a normative calculator to assess individuals affected by HD and identify and evaluate cognitive performance.

1.2. Secondary Aims

Further, the assessed cognitive assessment battery aims at the following points:

i. establishing and better defining a profile of cognitive alterations of HD and other neurological diseases for diagnostic purposes and
ii. assisting in continues monitoring and tracking disease progression and
iii. monitoring and evaluating the impact of therapeutic pharmacological and nonpharmacological interventions and evaluating the progress of the therapeutic regime chosen for the patient.

2. Methods

2.1. Study Design

The data from the observational Enroll-HD study (ClinicalTrials.gov Identifier: NCT01574053) was used in this study, a global clinical research platform designed to facilitate clinical research in HD (Sathe et al., 2021). The Enroll-HD is designed as a prospective longitudinal observational study collecting natural history data in HD, containing the gene-expansion carriers (HDGECs) and non-HDGEC controls, providing core phenotypic information.

The clinical data are collected annually from all research participants, including controls following the standardised study protocol. The Enroll-HD is designed as a multi-centre, multi-language prospective longitudinal observational study.

As the Enroll-HD study was established in July 2012, the collected data has generated a large and rich clinical database to support research and clinical activities. Data are monitored for quality using a risk-based monitoring approach.

2.2. Study Procedure

2.2.1. Study Population

The study population was built from the data set extracted from the periodic data set 4 (PDS4) of the Enroll-HD study, including 15,301 participants from 139 study sites across the world (Landwehrmeyer et al., 2017).

The Enroll-HD database includes two groups of participants: participants carrying the HD gene-expansion carriers (HDGECs), either at a clinically manifest or at a premanifest stage and participants known not to carry the *htt*-expansion mutation, i.e., HD family members who opted for predictive genetic testing and learnt that they are genotype-negative and family controls who were shown to carry a CAG repeat expansion within the physiological range at the *htt* gene by undisclosed genotyping, known as non-HDGEC expansion mutation.

2.2.2. Normative Data Set

For this study, only the data of the healthy controls, i.e., participants without comorbid conditions, under exclusion of neurological, psychiatric, internal and other acute and chronic conditions that may influence the cognitive performance, were selected.

The process of forming the normative data with multiple steps according to the predefined inclusion and exclusion criteria is described in Figure 22. Participants who have performed the neuropsychological test with uncorrected vision and hearing and not in the participant's first language were excluded from obtaining a proper normative supple for this study.

Moreover, participants for whom educational or language information was missing were excluded.

The full available set of the heath controls participants was in the next step examined to minimize a potential adverse impact of depressed mood on cognitive functioning, participants with evidence for an ongoing depression Hospital Anxiety Depression Scale score (HADS > 10 were excluded) (Zigmond and Snaith, 1983).

In addition, participants with evidence for cognitive impairment (MMSE ≤ 26) were excluded to minimize the effects of pathological ageing. In this process, the normative dataset was created and used for further analysis in this study. For feasibility control of the study results, the participants undergoing the whole cognitive battery, including following neuropsychological tests, SDMT, SWRT, SCNT, SIT; TMT-A, TMT-B, VFT, LFT, created a complete cognitive battery set.

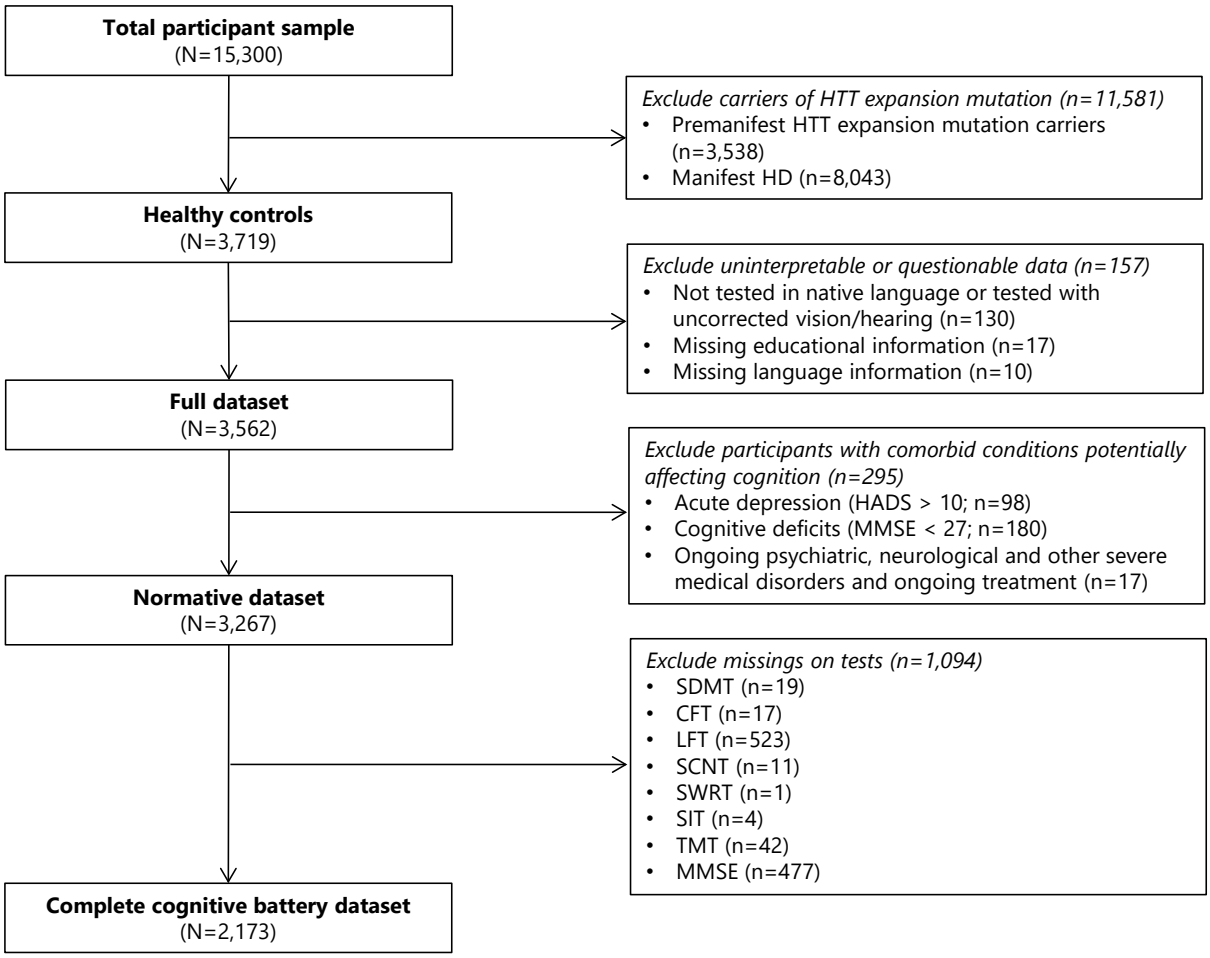


Figure 22: Flow chart describing the selection process defining a 'Normative Dataset'
The flow chart depicting the selection process defines a 'Normative Dataset' and a 'Complete Cognitive Battery Dataset'. The results reported in the main text are based on the Normative dataset (N=3,267). Results from the Complete cognitive battery dataset (N=1,173) and Full dataset (N=3,562) were used to check the robustness of the findings.

2.3. Study Assessments

For each participant who agrees to participate in the Enroll-HD study by signing an informed consent form at the respective site, the following assessments as listed in Table 18.

Study Assessments	
Sociodemographic Information:	Age Genetic Test (CAG) Disease Burden Score (DBS) Date of Test Date: HD clinical diagnosis Ethnicity Gender Marital status Living & caring situation Employment status Years of education
Medical history:	Comorbidities
Current HD-related Therapies:	Pharmacotherapy Nutritional Supplements Non-Pharmacologic Therapies
Functional Assessments:	UHDRS Total Functional Capacity UHDRS Functional Independence Scale
Motor Assessments:	UHDRS Total Motor Score UHDRS Diagnostic Confidence Index
Cognitive Assessment:	Symbol Digit Modalities Test Stroop Colour Naming Test Stroop Word Reading Test Stroop Interference Test Categorical Verbal Fluency Letter Verbal Fluency Trail Making Test A Trail Making Test B Mini-Mental Status Examination

Table 18: Study assessments overview for the normative data set
Note: UHRDS: United Huntington Disease Rating Scale. The number of CAG triplets (Cytosin, Adenosine, Guanin) referred to the severity of HD.

2.3.1. Informed Consent

Enroll-HD has been approved by the local institutional ethical review boards at every study site and conducted in accordance with the ethical standards described in the Declaration of Helsinki of 1964. All participants were informed about the study procedure and provided written informed consent for their participation prior to any study activities. Any information that could risk disclosing the identity of the participants examined was omitted.

2.3.2. Sociodemographic Information

For each participant who agrees to participate in the study, the following sociodemographic information, including age, gender, ethnicity, marital status, living and caring situation, employment status., years of education, was collected.

2.3.3. Medical History

Medical history regarding the comorbidities, including addictions and ongoing medications, particularly pharmacotherapy, in patients with relation to HD was collected. Further considering the HD diagnosis, the date of genetic test and the estimated date of the disease onset were recorded. In the genetic test, both alleles with a number of CAG were collected for the patient population.

2.3.4. Cognitive Battery

The cognitive state of participants was assessed by a comprehensive neuropsychological battery of the Enroll-HD consisting of the following tests: SDMT, SWRT, SCNT, SIT; CLF, LVF; TMT-A, TMT-B and MMSE. In the following, these neuropsychological tests will be explained in more detail.

Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) (Smith, 1982) assessed the psychomotor speed and working memory. The first digits (1-9) assigned to symbols were presented to the participants during this assessment. In the second step, the participants were required to write below each presented symbol the correct corresponding digit. The number of correct matches completed in 90 seconds was recorded.

Stroop Word Reading Test

This assessment has very good properties for detecting a cognitive decline in the early stages of HD as it measures attention and psychomotor speed. This assessment is a subtest of the Stroop tests (Stroop, 1935, Golden, 1978). During this assessment, the participant was asked to read words indicating colours (red, blue, green) printed in black ink as quickly as possible; the time limit was 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Stroop Color Naming Test

The Stroop Colour Naming Test (SCNT), as part of the Stroop tests, has very good properties for detecting a cognitive decline in the early stages of HD as it measures attention and psychomotor

speed (Stroop, 1935, Golden, 1978). During this assessment, the participant was asked to read the colour of ink patches on the template (e.g., green, blue, red) as quickly as possible; the time limit was 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Stroop Interference Test

The Stroop Interference Test (SIT), as the third subtest, is used to measure response inhibition (Golden, 1978). The participants see words indicating colours (red, blue, green), each written in red, blue or green ink, incongruent to the colour indicated by the letters (e.g., the word 'red' written in blue ink). Participants have to inhibit uttering the words read and instead have to name the colour of the ink in which the incongruent colour names are printed. If possible, the time limit was 45 seconds. Total correct answers (correctly named items), total errors and total self-corrections performed in 45 seconds were recorded.

Letter Verbal Fluency

The Letter Fluency Test (LFT) measures mental flexibility and semantic knowledge (Benton and Hamsher, 1976). In the LFT, participants were requested to utter as many words as possible, starting with a particular letter within one minute (response is speech motor output). LFT consists of three sub-tests, each using a different letter (i.g. S, M, T in German), tapping into the categories of high, medium and low frequency in the lexicon of the respective language (Senft, 2008). The total score as the sum of the correct, unique words of all sub-tests was recorded. The repetitive words count only once.

Categorial Verbal Fluency

In the Categorial Fluency Test (CFT), which is used to measure verbal learning and recall processes, participants are asked to name as many different words from the category "animals " as possible in one minute (Benton and Hamsher, 1976). The sum of correctly named words – animals were recorded.

Trail Making Test – Part A

The Trail Making Test (TMT) consists of A and B tasks, drawing straight lines connecting appropriate circles (Reitan, 1955). The TMT-A measures psychomotor speed. The rules for connecting circles labelled with numbers or letters differ between the two tasks: In the TMT-A, participants must connect given numbers in ascending order (i.e., 1-2-3-4), from 1 till 25. The time to complete the

task is measured as a primary outcome, the number of failures or self-correction is also reported. TMT-A is an ideal measure of psychomotor speed.

Trail Making Test – Part B

The Trail Making Test – Part B (TMT-B) is the second task on the TMT with drawing straight lines connecting appropriate circles labelled with numbers and letters (Reitan, 1955). In the TMT-B, participants must connect given numbers and letters in alternating order (i.e., 1-A-2-B-3-C;). Thereby, the TMT-B taps executive and visual-perceptual functions, such as cognitive flexibility and selective attention abilities (Tombaugh, 2004). The time to complete the task is recorded as a primary outcome, the number of failures or self-correction is also reported.

Mini-Mental Status Examination

The Mini-Mental State Examination (MMSE) is a short screening questionnaire consisting of eleven tasks measuring five areas of cognitive function: orientation, registration, attention and calculation, recall and language. The MMSE is a 30-point test, quick in the administration (5 minutes). It is widely used in clinical and research settings to assess general cognitive functioning and screen for pronounced cognitive decline. Higher scores indicate better cognition. The MMSE is applied as per the standard operating procedure of the original publication (Folstein et al., 1975).

2.4. Statistical Analysis

2.4.1. Descriptive Analyses

Descriptive statistical methods were applied to describe the normative data set consisting of participants and their demographic characteristics. Continuous variables were characterized by means (*M*), standard deviations (*SD*), medians and ranges. Categorical variables were expressed as percentages to the whole sample. Table norms consisting of *M* and *SD* stratified by age, education level (≤12 years and >12 years of education), gender and language were constructed when feasible. Education years were dichotomized for the table norms to establish a lower (≤12 years) and higher (>12 years) educated group of participants. This dichotomization allows considering the different education levels while keeping the norms easy to read. A similar approach has been used to create norms in Alzheimer's disease in the project memory clinic (Beeri et al., 2006) and published by Mills et al. for HD (Mills et al., 2020).

2.4.2. Development of Normative Values

General Approach and Model Selection

Choosing a proper model for this study was based upon the rationale that the developed normative values need to consider the impact of age, gender, language and education level on the scores obtained from the examined neuropsychological test (SDMT, SWRT, SCNT, SIT, TMT-A and B, CFT, VFT). The final decision also accounted for the possible missing values on the psychological test scores. As expected, several parameters, e.g. age, in the study have a nonlinear relation to the neuropsychological test scores, making Linear Multiple Regressions (LMRs) models with age, education years, language and gender as predictors inappropriate. Literature utilising regression-based norming has considered nonlinear relationships by including both age and age^2 as predictors in the regression models (Van Breukelen and Vlaeyen, 2005, Smerbeck et al., 2012, Argento et al., 2016). However, quadratic models are likely to be less appropriate than other nonlinear models when modelling the development of abilities or performance with maturing or ageing, or abilities often exhibit threshold effects (Williams et al., 2019).

Furthermore, Generalized Additive Models (GAMs), including all predictors and using tensor splines to model possibly nonlinear additive effects of age and years of education, may also be used to establish the normative values (Wood et al., 2012). To evaluate the predictive performance of each demographic variable, models were fitted using either all four predictors or dropping one predictor at a time. Models were subsequently compared via leave-one-out information criterion (LOO-IC) as an approximate measure of expected predictive accuracy. In the further steps of this study, multiple nonlinear Bayesian regression analysis approaches were run between the studied cofounding parameters, such as age, gender, education level and language and scores of the neuropsychological test of the studied cognitive battery to determine the model of best fit. A normative probability mapping approach extended to behavioural data was chosen as the best appropriate approach (Marquand et al., 2016, Wang et al., 2020).

2.4.3. Bayesian Model

This study uses the Bayesian approach for statistical analysis. Bayesian modelling provides information about the probability of the model parameters made as a combination of the predictions about the parameters and what is learned about the parameters from the data (Baldwin and Larson, 2017). The prediction about the probability of the parameters is known as the "prior" as it represents the parameter predictions prior to processing the data. In contrast, combining the

prior and the data (Equation 2) produces the posterior distribution because it is created after seeing the data (Baldwin and Larson, 2017).

$$P\ (parameter|data) = \frac{P\ (data\,|\,parameter)\ \ P(parameter)}{P(data)}$$

Equation 2: Bayesian Theorem
The Conditional probability – Bayes Theory where p (parameters) is the prior and p (parameters /data) is the posterior (read as the probability of the parameters given the data)

The posterior distribution offers a major difference between Bayesian and classical statistical analysis (frequentist models) that compute probability as the end product with a single number or point estimate, reporting a standard error or a confidence interval to give a sense of the probability in the samples (Cohen, 1988). In contrast, by computing this probability from a Bayesian perspective, the end product is a distribution or density, making it a more suitable approach for normative studies (Baldwin and Larson, 2017).

Based on the Bayesian modelling, estimation of a normative distribution of the cognitive test scores at different levels of relevant sociodemographic variables (e.g., age, gender, language and education level) will be done. The normative distribution is used to predict an outcome of a single individual based on their above-mentioned sociodemographic characteristics. A graphical solution to display the posterior distribution is used because graphs display a wealth of information (e.g., the most probable values, the degree of skewness, and the degree of uncertainty) in a compact form, allowing the reader to gain more intuitive access to the results than a table could potentially offer.

Normative Probability Maps

Predictions of new subjects' neuropsychological test scores and cognitive performance were performed by normative probability maps (NPM) and global z-scores (Wang et al., 2020). In summary, the NPM combines three sources of information: 1) the error (difference between true and predicted responses); 2) the predictive variance of the test point; and 3) the variance of the normative data (Ziegler et al., 2014). This approach was chosen as the model accommodates the data distribution. Predictions made in regions with a low density or high spread of points will have appropriately low predictive precision (high variance). This feature is important in the context of this study, as a study cohort was not always covering the complete range of the covariates of interest. In this case, the individuals from the end range of the neuropsychological testing should be recruited, ideally to have a large sample with good coverage of the full range, but this may not be possible

(e.g., because it may require recruiting many low-functioning patients), however the NPM approach guarantees that uncertainty is handled coherently, regardless of the context (Ziegler et al., 2014). By integrating the observed expectation error and the predictive uncertainty, the local maps and global scores exploit the advantages of Bayesian inference for clinical decisions and provide a valuable extension of diagnostic information about pathological ageing and other cofounding parameters (Ziegler et al., 2014).

In this study, a method of normative probability mapping to construct normative *z* scores for each of the included cognitive measures (Ziegler et al., 2014, Marquand et al., 2016, Wang et al., 2020). The *z* score on test *j* was calculated as shown in Equation 3 for each individual i.

$$z_{ij} = \frac{y_{ij} - \hat{y}_{ij}}{\sqrt{\sigma_{ij}^2 + \sigma_{nj}^2}}$$

Equation 3: Construction of z scores
The z score on test j is calculated for each individual i. The individual's actual score is y_{ij}, and further $\hat{y}_{ij}$ is the individual's mean predicted score, σ_{ij}^2 is the variance of predictive distribution for the individual i and $\sigma_{nj}^2$is the residual variance of the model for cognitive measure j.

Since TMT-A and TMT-B are reverse coded, whereby lower scores indicate better performance, *z* scores for these two measures were multiplied by minus one to keep interpretation consistent with the rest of the measures. In the last step, a difference between predicted and observed values is calculated and scaled by the model's residual variance to yield a *z*-value with zero mean and unit standard deviation concerning the normative sample.

2.4.4. Analysis of Cognitive Differences Based on Gender and Language

An analysis of the difference in gender and different language groups was performed by comparing the models generated to develop regression-based norms. In this matter, the gender differences in cognitive performance were assessed by examining the posterior parameter distributions of models that included all predictors, i.e. age, education, gender and language. All differences were reported as positive values indicating higher scores for females than males and vice versa. Furthermore, a two-step approach was carried out to evaluate differences in cognitive performance across the different language groups.

2.4.5. Comparison between Full Model to Leave-One-Out Information Criterion Model

The full models containing all predictors were compared to models containing only age, education and gender (missing language information) in the first step. This process is based on establishing the Leave-One-Out Information Criterion (LOO-IC) model to estimate a measure of expected predictive accuracy. The means and 95% confidence intervals (CI) were reported to describe the different LOO-IC models. A difference was considered to be significant if the 95% CI did not contain zero. If the model comparison evaluation showed that the full model containing all predictors performed better predictive performance than the LOO-IC model, the parameter estimates of the full models were subsequently examined in a second step. In this part of the analysis, additional model parameters were estimated by their means and 95% highest density posterior probability intervals (PPI), i.e., the shortest interval with a 95% probability of containing the true parameter value.

All models were estimated using the "Stan" software, version 2.19 (R, 2019) accessed via the "brms" package in the R language (Bürkner, 2017). Due to their positive skewness, TMT-A and TMT-B were log-transformed prior to the inclusion in the analysis.

2.4.6. Markov Chain Monte Carlo Methods

In the next step, the Markov chain Monte Carlo method (MCMC) was used to describe the insights of the models. In Bayesian statistics, the recent development of MCMC methods has made it possible to compute large hierarchical models, such as in this study required for the integrations of a larger number over hundreds to thousands of unknown parameters (Banerjee et al., 2014). In summary, MCMC methods comprise a class of algorithms for sampling from a probability distribution. By constructing a Markov chain with the desired distribution, it is possible to obtain a sample of the desired distribution by recording states from the chain (Banerjee et al., 2014). The more steps involved in the process, the more accurately the distribution of the sample corresponds to the actual desired distribution. There are different algorithms for chain construction. In this study, each model was estimated using a method of the Hamiltonian Monte Carlo sampling algorithm with four chains consisting of 2000 iterations, out of which 1000 iterations were discarded as a warm-up resulting in the final sample of 4000 draws from the posterior distribution.

2.4.7. Evaluation of the Bayesian Model

After fitting a Bayesian model, it is essential to measure predictive accuracy. This can be performed using Bayesian cross-validation methods to ensure the good predictive performance of the fitted model (Vehtari et al., 2017). This study estimated all models using average likelihood and non-informative improper flat priors over predictor parameters. After this evaluation, weakly informative priors for model intercepts and parameters' standard deviations were used to ensure proper convergence. The quality of the sampling algorithm was checked both numerically by inspection of the potential scale reduction factor ($\hat{R}s$) and visually by inspection of trace plots and posterior predictive probability plots (Muth et al., 2018). In the final step, proof of weighting was performed as it is a convenient general way to adjust for draws from the wrong distribution, so the models' results were for influential observations using Pareto $\hat{k}$ statistic, which is a method for stabilizing importance weights using a generalized Pareto distribution fit to the upper tail of the distribution of the simulated importance ratios (Vehtari et al., 2017, Vehtari et al., 2021).

2.5. Normative Calculator

An interactive normative calculator was created as a server-based web application to efficiently evaluate the patients' cognitive performance in daily clinical practice and research. The normative calculator uses look-up tables created from the above models containing every possible combination of values: z-scores, derived from the scores of the neuropsychological tests SDMT, SWRT, SCNT, SIT, TMT-A and TMT-B, CFT and VFT and demographic variables (i.e., age, gender, education level, language). The web application provides a user interface to transform the measured (raw) values from the neuropsychological tests into *z*-scores using these lookup tables.

The application of normative calculators can be explained with a practical example. In contrast to the measured (raw) values, a z-score allows an immediate interpretation of the result from the neuropsychological tests. By shifting the distribution of the test score to a mean (M) of zero and scaling it to a standard deviation (SD) of one, a measured test score can be considered "in the normal range'', if the corresponding z-score is no more than one standard deviation away from zero, i.e. between -1 and 1. Without further information, it may be unclear how to classify, e.g. a raw value of 60 symbols measured in the SDMT, corresponding with a z-score of 0.64, and refer to a slightly above average result, though still within the normal range. To emphasize that immediate applicability, a colour-coded interpretation of the resulting percentile is added, e.g. “superior” (green) “, the average” (yellow) or “severely impaired” (red).

All researchers and clinicians can freely access and use the interactive web-based normative calculator on the following website: https://nc.2mt-software.de. After entering a patient's demographic data and measuring raw values for each neuropsychological test, the normative calculator automatically provides the corresponding *z*-scores and percentiles.

To foster the ability to analyse large data sets, the web application also offers the ability to upload CSV formatted tables (e.g. exported by MS Excel) and calculate the z-Scores and percentiles for the whole file.

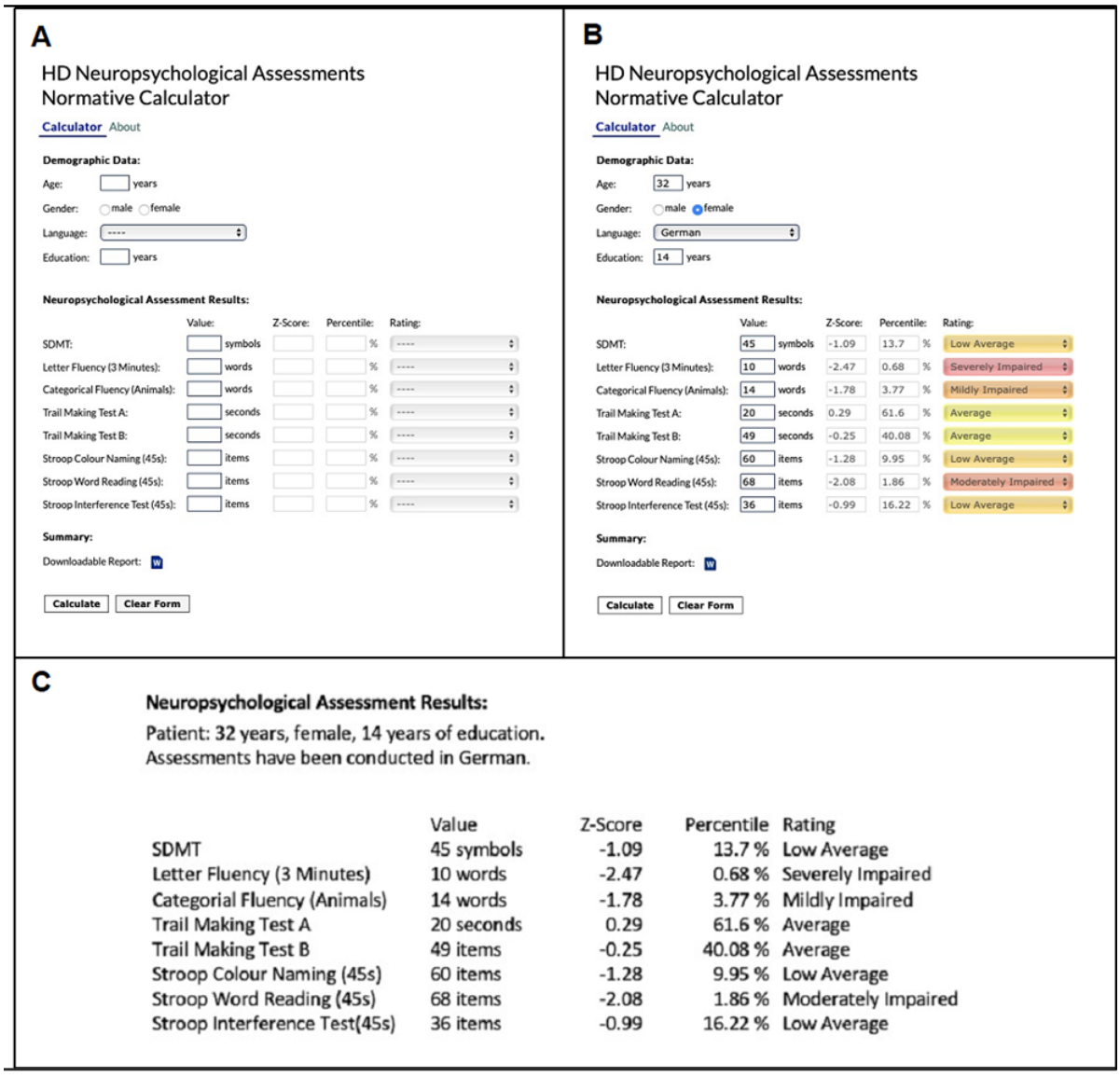


Figure 23: The normative calculator
From upper left to right: A) Entry forms (demographics and raw values obtained for each cognitive test) with automatic export function including a downloadable report in RTF format, B) Example output for a 32-year old HD patient, C) Downloadable report in RTF-format

3. Results

3.1. Demographic Characteristics of the Normative Sample

Normative Sample (NS) used in this study consist of a cohort of *N* = 3,267 (1,978 females, 1,289 males) healthy controls with a mean age of *M* = 46.99 years (*SD* = 14.61, ranging from 18 to 86) and an average number of education years of *M* = 14.66 (*SD* = 3.27, ranging from 1 to 24 educations years).

The cognitive battery consisting of the neuropsychological assessments included SMDT, SWRT, SCNT, SIT, TMT-A and TMT-B, CFT, VFT were administered in the following languages (in descending order of frequency): English, German, Spanish, Italian, Polish, French-Canadian, French, Dutch, Spanish Latin-American. Demographic characteristics of the normative sample are displayed in Table 20.

The descriptive statistics on the performance of the normative sample (*N* = 3,267) in the cognitive battery consisting of the neuropsychological tests as described in Table 19.

Cognitive performance measures	*N*	*M*	*SD*	Median	Range
Symbol Digit Modalities Test	3248	50.7	11.7	51.0	0–101
Category Fluency Test	3243	22.2	5.5	22.0	3–48
Stroop Tests					
Stroop Color Naming Test	3237	75.4	14.1	75.0	0–140
Stroop Word Reading Test	3242	96.4	17.1	98.0	2–168
Stroop Interference Test	3059	43.2	11.2	43.0	0–119
Trail-Making Tests					
TMT-A	2759	27.1	15.1	24.0	8–240
TMT-B	2754	57.6	32.7	49.0	16–240
Letter Fluency Test	2726	41.6	12.4	41.0	7–94
MMSE	2355	29.3	0.9	30.0	27–30

Table 19: Descriptive statistics of normative sample in neuropsychological assessments
Description of the cognitive performance on neuropsychological assessments of the normative sample (N = 3,267) showing as N = number of participants in each group; M = mean; SD = standard deviation; Symbol Digit Modalities Test (min.-max.: 0–110 points in 90 sec); Category Fluency Test (number of correct words in 60 sec); Letter Fluency Test (number of correct words for three letters in 60 sec each, i.e. in total 180 sec); Trail Making Test, Part A; TMT-B = Trail Making Test, Part B (both TMT-A and -B time in sec, max. 240 sec, the longer time elapsed, the worse performance); Stroop test in each condition (min.-max.: 0–200 in 45 sec); MMSE = Mini-Mental State Examination (min.-max.: 0–30 points).

Demographic Description		
	Normative Sample (N = 3,267)	N (%)
Age	18-25	209 (6.4)
	25-29	256 (7.8)
	30-34	323 (9.9)
	35-39	321 (9.8)
	40-44	310 (9.5)
	45-49	344 (10.5)
	50-54	396 (12.1)
	55-59	368 (11.3)
	60-64	323 (9.9)
	> 64	417 (12.8)
Gender	Female	1978 (60.5)
	Male	1289 (39.5)
Education levels	ISCED 0	5 (0.1)
	ISCED 1	76 (2.3)
	ISCED 2	273 (8.4)
	ISCED 3	890 (27.2)
	ISCED 4	704 (21.6)
	ISCED 5	1227 (37.6)
	ISCED 6	92 (2.8)
Education years	≤ 12 years	852 (26.1)
	> 12 years	2415 (73.9)
Laterality	Right-handed	2933 (89.8)
	Left-handed	253 (7.7)
	Mixed	81 (2.5)
Language	English	1808 (55.3)
	German	639 (19.6)
	Spanish	299 (9.2)
	Italian	238 (7.3)
	Polish	98 (3.0)
	Canadian French	70 (2.1)
	French	21 (0.6)
	Dutch	46 (1.4)
	Latin American Spanish	29 (0.9)
	Danish	19 (0.6)
Ethnicity	Caucasian	3031 (92.8)
	American Black	28 (0.9)
	Hispano or Latino Origin	81 (2.5)
	American Indian/Native American/Amerindian	18 (0.6)
	Asian	19 (0.6)
	Mixed	44 (1.4)
	Other	46 (1.4)

Table 20: Demographic characteristics of the normative sample
The complete Normative Sample (NS) consist of N = number of participants in each group; ISCED = International Standard Classification of Education; ISCED 0 = Early childhood education; ISCED 1 = Primary Education; ISCED 2 = Lower Secondary Education; ISCED 3 = Upper Secondary Education; ISCED 4 = Post-secondary non-Tertiary Education; ISCED 5 = Short-cycle tertiary education; ISCED 6 = Bachelor's degree or equivalent tertiary education level

All statistical analyses were performed on both the full dataset (*N*=3,562). The process of defining the full data sets and other data sets is displayed in Figure 22. Further analyses were performed on the more restricted dataset (*N*=2,173), in which only participants who completed the whole cognitive battery were included. These additional analyses were performed to check for the generality of the statistical method and are not included in this thesis but may be provided upon request. The results from both data sets showed equivalent results.

3.2. Regression-based Normative Values

In the analysis, all applied models were converged within a certain number of iterations ($\hat{R}s < 1.01$), and in this process, no influencing observations were present based on Pareto statistics (Pareto $\hat{k}s < 0.5$). Across all tests, the GAMs models showed better performance than the LMRs, as shown in Table 21. This table presents the most important combinations of the predictors consisting of age, gender, education years and language in parallel comparison for the GAM and LMR model. In the model selection, validation was performed by the leave-one-out information criterion (LOO-IC), a method for estimating pointwise out-of-sample prediction accuracy. The values represent LOO-IC and its standard deviation; however, the smaller values of LOO-IC indicate a better fit of the model, meaning the predictive performance abilities.

In the further analysis, the GAM model, including all variables (age, gender, education years and language), showed better predictive performance on the following neuropsychological tests SDMT, SCNT, TMT-A and LFT. The model without gender showed better predictive performance on these measures CFT, SWRT, SIT and TMT-B. After posterior prediction testing, the models' predictions agreed well with the observed data as displayed in the figure.

Comparison of models for regression-based z-scores calculation									
Included predictors	Model type	SDMT	Category Fluency	Stroop Color Naming	Stroop Word Reading	Stroop Interference	TMT-A	TMT-B	Letter Fluency
age + edu + lan + gen	LMR	23,937.19 (112.75)	19,964.73 (91.61)	25,908.32 (105.84)	27,201.27 (110.30)	22,784.53 (136.48)	1,865.05 (134.49)	2,507.29 (89.57)	21,101.89 (76.94)
	GAM	23,862.85 (114.91)*	19,939.03 (92.36)	25,863.26 (107.09)*	27,126.16 (110.42)	22,749.68 (139.96)	1,801.90 (137.89)*	2,403.16 (90.76)	21,077.55 (76.96)*
age + edu + lan	LMR	24,005.04 (111.45)	19,966.89 (91.39)	25,911.38 (105.85)	27,201.41 (110.30)	22,785.86 (136.19)	1,864.91 (134.09)	2,508.28 (89.66)	21,109.60 (76.84)
	GAM	23,926.45 (113.56)	19,938.69 (92.25)*	25,864.98 (107.24)	27,124.15 (110.46)*	22,749.64 (139.86)*	1,802.61 (137.35)	2,402.11 (90.84)*	21,083.56 (76.88)
age + edu + gen	LMR	24,083.49 (108.82)	20,003.53 (90.16)	25,974.03 (105.74)	27,271.01 (106.67)	22,815.86 (135.19)	2,062.25 (125.00)	2,706.08 (88.95)	21,167.00 (76.53)
	GAM	23,983.17 (111.85)	19,974.61 (91.00)	25,924.09 (106.59)	27,201.02 (107.06)	22,782.65 (138.48)	1,964.28 (128.84)	2,559.34 (89.92)	21,130.12 (76.40)
age + lan + gen	LMR	24,245.68 (111.32)	20,138.20 (90.66)	26,025.43 (102.82)	27,412.77 (107.81)	22,939.38 (133.40)	1,957.77 (131.55)	2,703.40 (90.11)	21,337.21 (74.75)
	GAM	24,176.60 (112.48)	20,019.18 (92.00)	25,974.00 (104.41)	27,365.51 (108.42)	22,895.64 (137.06)	1,895.90 (135.30)	2,605.75 (91.50)	21,314.24 (75.21)
edu + lan + gen	LMR	24,697.14 (101.58)	20,019.18 (92.00)	26,100.68 (103.18)	27,352.21 (107.55)	23,244.06 (118.61)	2,277.46 (120.43)	2,879.00 (88.44)	21,099.87 (76.85)
	GAM	24,618.33 (102.54)	20,011.37 (92.09)	26,075.64 (103.24)	27,279.93 (107.01)	23,213.89 (120.26)	2,227.68 (120.58)	2,810.77 (89.22)	21,084.19 (76.72)

Table 21: Comparison of models for regression-based z-scores calculation

*Values represent leave-one-out information criterion (LOO-IC), and its standard deviation (in brackets), smaller values of LOO-IC indicate better fit; *models with the best fit according to LOO-IC are presented in bold; edu = education; lan = language; gen = gender; LMR = linear multiple regression; GAM = Generalized Additive Model; SDMT = Symbol Digit Modalities Test, TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B.*

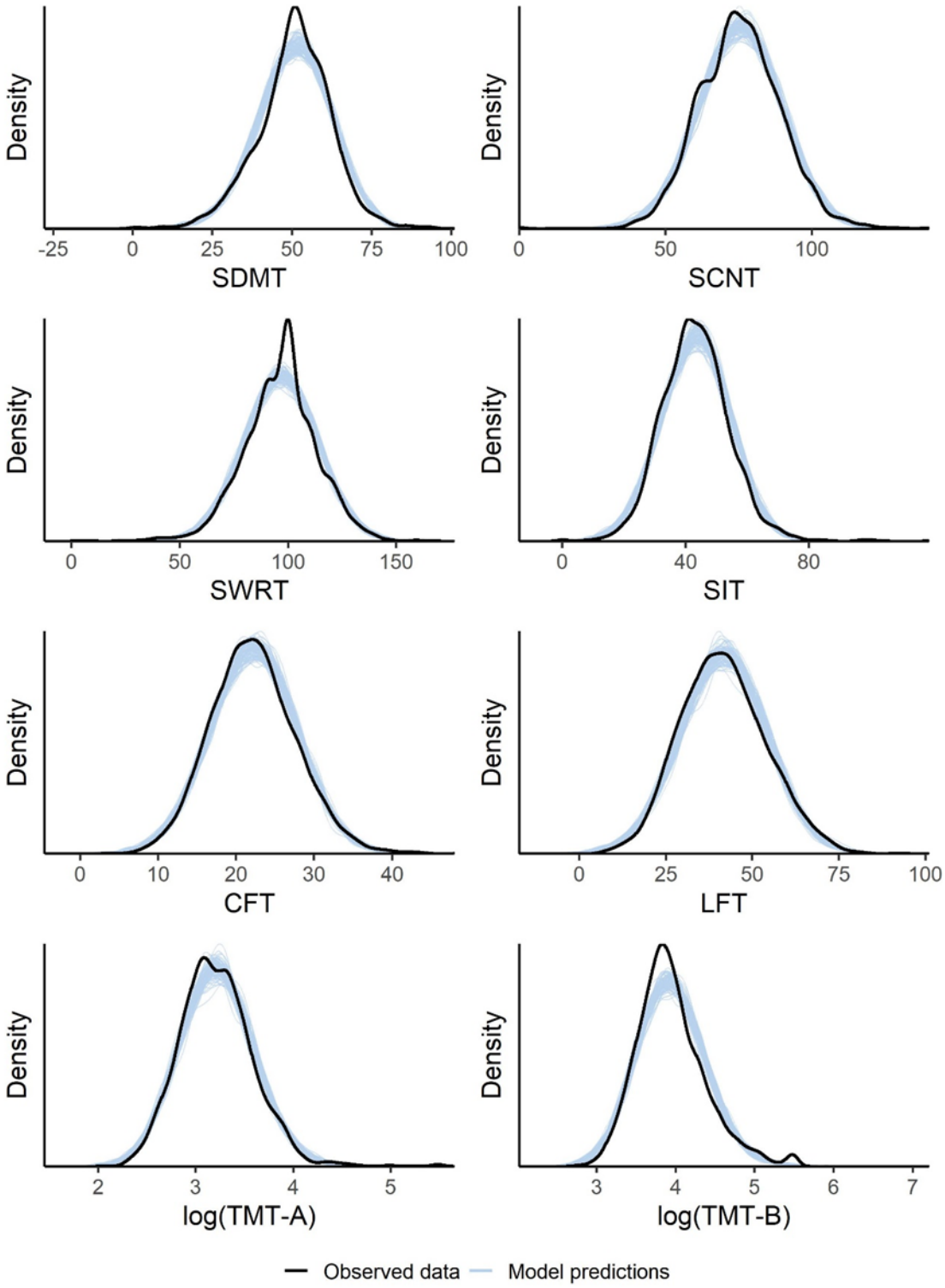


Figure 24: Posterior predictive checks of models used to generate normative z-values

3.3. Relationship between Age and Cognitive Performance

The relationship between age and performed cognitive tests is presented in Table 22, stratified by age in years. The obtained values refer to the posterior means within the 95% posterior probability intervals for different age groups.

Posterior mean values for each cognitive test stratified by age								
Age	SDMT	CFT	SCNT	SWRT	SIT	TMT-A	TMT-B	LFT
20	56 [55,58]	23 [22,24]	78 [76,80]	99 [97,102]	48 [47,50]	22 [21,23]	46 [43,49]	41 [39,43]
30	55 [54,56]	23 [22,23]	78 [77,80]	99 [97,100]	47 [46,48]	22 [22,23]	47 [45,49]	42 [40,43]
40	53 [52,54]	23 [22,23]	77 [76,79]	98 [96,100]	46 [45,47]	24 [23,24]	48 [46,51]	42 [41,44]
50	50 [49,51]	22 [22,23]	76 [74, 77]	96 [95,98]	43 [42,44]	25 [25,26]	52 [50,54]	43 [41,44]
60	46 [45,47]	22 [21,22]	72 [71,74]	93 [91,95]	39 [38,41]	29 [28,30]	59 [57,62]	42 [41,43]
70	41 [39,42]	20 [20,21]	68 [66,69]	88 [86,90]	35 [34,36]	34 [32,36]	73 [70,78]	41 [39,42]
80	34 [31,37]	18 [17,20]	62 [58,65]	82 [78,86]	30 [27,32]	43 [39,47]	100 [89,113]	39 [36,42]
90	27 [21,32]	16 [13,19]	55 [48, 61]	76 [67, 83]	24 [18, 29]	55 [45, 69]	143 [112,185]	37 [30,42]

Table 22: Posterior mean values for each cognitive test stratified by age
Values represent posterior means and their 95% Posterior Probability Intervals (PPI, in brackets) for different years of age (rows), grand mean for gender and language and education set on sample median (i.e., 14 years), SDMT = Symbol Digit Modalities Test, CFT = Category Fluency Test, SWRT= Stroop Word Reading Test, SCNT = Stroop Color Naming Test, SIT = Stroop Interference Test, TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B, LFT = Letter Fluency Test. Age in years.

Figure 25 displays an overview of the relationship between age and performance in cognitive tests in the posterior predictive plot. Blue lines refer to the expected cognitive performance in the different neuropsychological tests for different age groups under the constraint of assuming 14 years of formal education while refraining from specifying gender and language used during the examination. The grey bands represent 95% posterior predictive intervals, and dots represent observed values. A nonlinear decline was detected in performance with advancing age for all cognitive tests when adjusting for education, gender and language. However, for CFT and LFT, a shallow decline was found. We observed an accentuated age-related decline in cognitive performance in all tests, with the decrease in performance being more pronounced in later decades than in earlier decades.

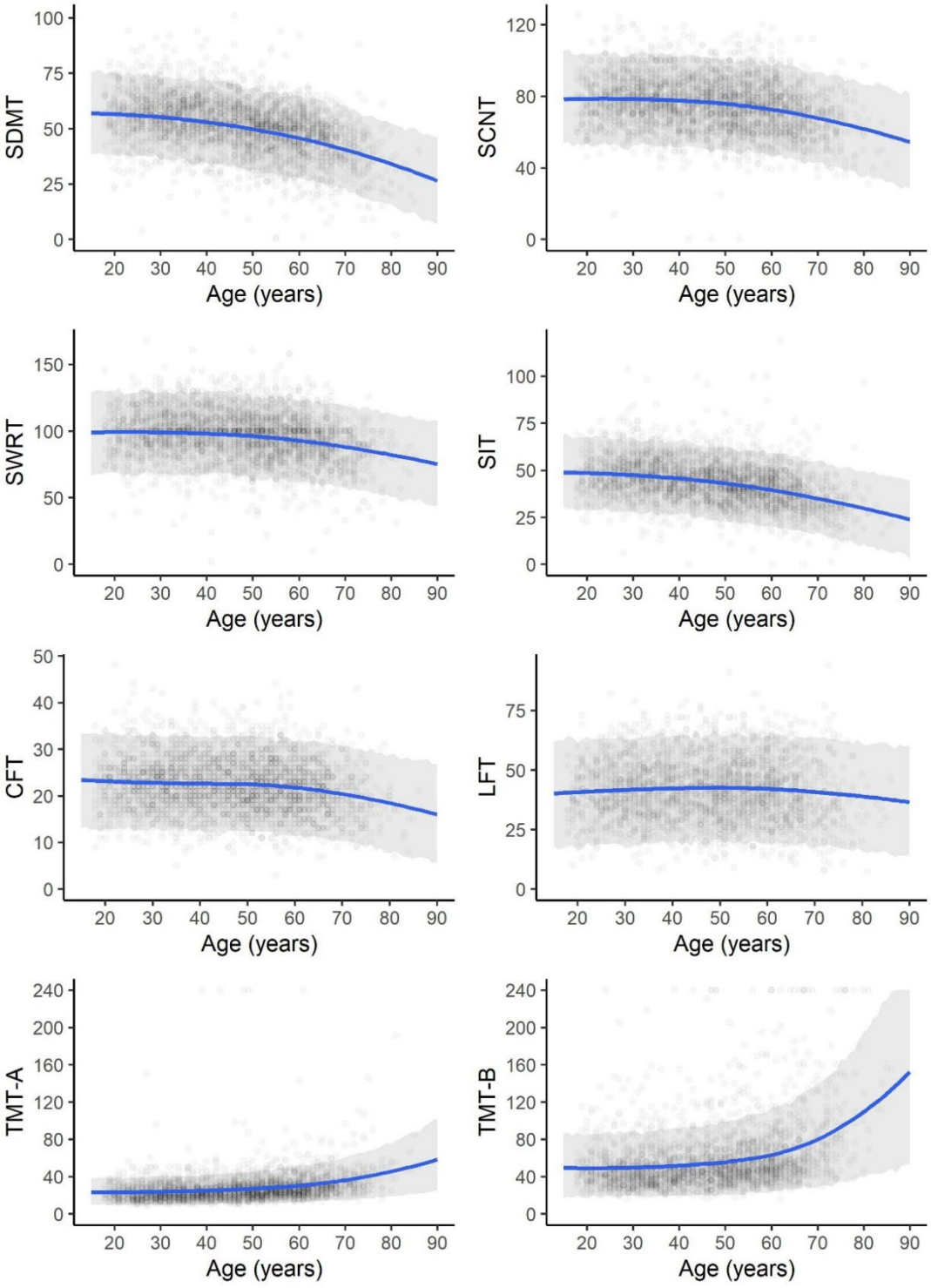


Figure 25: Posterior predictive plot depicting the relationship between age and performance in cognitive tests
The posterior predictive plot presents the relationship between age and performance in cognitive tests (raw values). Blue lines represent the expected cognitive performance in raw values for different years of age under the constraint of assuming 14 years of formal education while refraining from specifying gender and language used during the examination; grey bands represent 95% posterior predictive intervals, and dots represent observed values.

3.4. Relationship between Years of Education and Cognitive Performance

The association between education and cognitive performance is presented in Table 23. As expected, there is a positive correlation between performance and years of formal education for all cognitive tests. More extended education level was associated with better cognitive performance when adjusting for education, gender and language.

Posterior mean values for each cognitive test stratified by years of education								
Education	SDMT	CFT	SCNT	SWRT	SIT	TMT-A	TMT-B	LFT
8	42 [40,43]	20 [19,21]	70 [68,72]	86 [84,89]	38 [37,40]	30 [28,32]	69 [65,74]	34 [32,36]
10	46 [44,47]	21 [20,21]	72 [71,74]	91 [89,93]	40 [39,41]	27 [26,29]	61 [58,64]	37 [36,39]
12	48 [47,49]	22 [21,22]	74 [73,76]	94 [93,96]	42 [41,43]	26 [25,27]	55 [53,58]	40 [39,41]
14	50 [49,51]	23 [22,23]	76 [75,77]	97 [95,98]	44 [43,45]	25 [24,26]	51 [49,53]	43 [41,44]
16	52 [51,53]	23 [23,24]	78 [76,79]	100 [98,101]	45 [44,46]	24 [23,25]	48 [46,50]	45 [44,46]
18	53 [52,54]	24 [23,25]	79 [77,80]	102 [100,104]	46 [45,48]	23 [22,24]	46 [44,48]	47 [45,48]
20	55 [53,56]	25 [24,25]	80 [78,81]	103 [101,105]	47 [46,49]	23 [22,24]	45 [43,47]	48 [46,49]
22	56 [54,57]	25 [24,26]	81 [79,83]	103 [100,106]	48 [46,49]	23 [22,25]	45 [42,48]	49 [47,51]

Table 23: Posterior mean values for each cognitive test stratified by years of education
The values represent posterior means and their 95% Posterior Probability Intervals (PPI, in brackets) for different years of education (rows), grand mean for gender and language and age set on sample median (i.e., 48 years). SDMT = Symbol Digit Modalities Test, CFT = Category Fluency Test, SWRT= Stroop Word Reading Test, SCNT = Stroop Color Naming Test, SIT = Stroop Interference Test, TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B, LFT = Letter Fluency Test. Age in years.

For all tests, non-linearity was observed for the relationship between education level in years and cognitive performance, with the effects weakening with increasing years of education as displayed in Figure 26. The blue lines represent expected cognitive performance for different years of formal education. The most narrowing effect was observed in TMT-A.

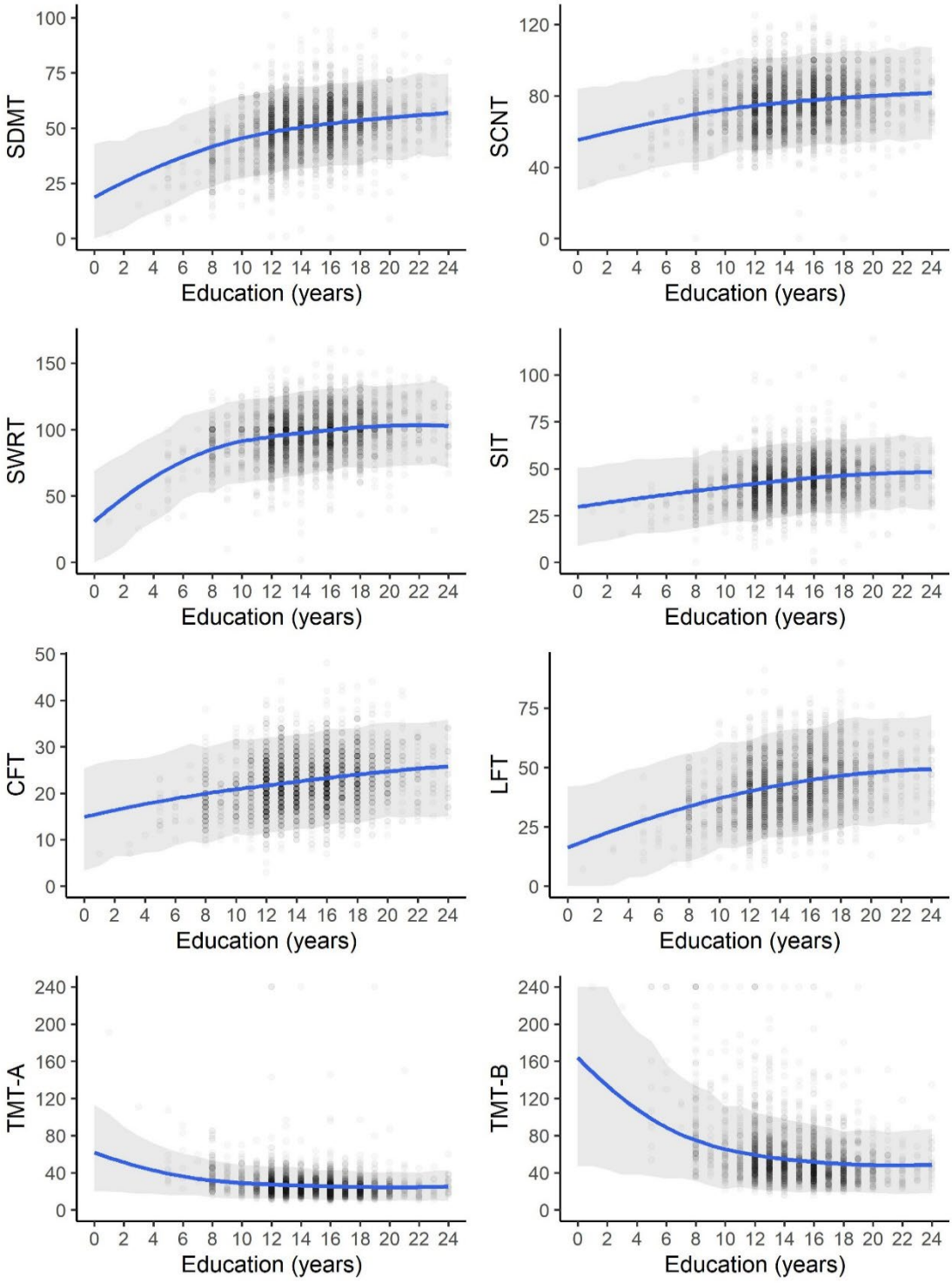


Figure 26: A posterior predictive plot of the relationship between years of formal education and performance in the cognitive test

Blue lines represent the expected cognitive performance for different years of formal education under the constraint of assuming a participant of 48 years of age while refraining from specifying gender and language used during the examination; grey bands represent 95% posterior predictive intervals, and dots represent observed values

3.5. Gender-related Differences in Cognitive Performance

The association between education and cognitive performance is presented in Table 24. To evaluate the impact of gender on cognitive performance, the data were first adjusted for education, gender and language, indicating that females performed significantly better than males in SDMT (*M* = 2.78, 95% PPI [2.07, 3.44]). Additionally, females displayed a slightly better performance than males in SCNT (*M* = 0.94, 95% PPI [0.03, 2.00]) and LFT (*M* = 1.33, 95% PPI [0.41, 2.20]), while males performed slightly better than females in TMT-A (*M* = 1.02, 95% PPI [1.00, 1.05]) and TMT-B (*M* = 0.98, 95% PPI [0.95, 1.01]). No clear gender-related differences were observed in CFT (*M* = 0.32, 95% PPI [-0.09, 0.69]), SWRT (*M* = 0.59, 95% PPI [-0.51, 1.81]) and SIT (*M* = 0.50, 95% PPI [-0.19, 1.28])

Differences in cognitive performance stratified by gender		
	female	male
SDMT	46.44 [44.66, 48.20]	43.65 [41.76, 45.30]
CFT	21.52 [20.60, 22.37]	21.20 [20.29, 22.07]
SCNT	71.66 [69.17, 73.79]	70.72 [68.42, 73.05]
SWRT	86.69 [83.54, 89.60]	86.10 [83.01, 89.27]
SIT	40.81 [39.00, 42.43]	40.31 [38.64, 42.03]
TMT-A	30.79 [28.55, 33.05]	30.14 [27.93, 32.35]
TMT-B)	66.41 [61.51, 71.86]	67.71 [62.54, 73.32]
VFT	39.30 [37.31, 41.44]	37.97 [35.75, 39.97]

Table 24: Posterior mean values for each cognitive test stratified by gender
The values represent posterior means and their 95% Posterior Probability Intervals (PPI, in brackets) for both gender, education, gender and language, SDMT = Symbol Digit Modalities Test, CFT = Category Fluency Test, SWRT= Stroop Word Reading Test, SCNT = Stroop Color Naming Test, SIT = Stroop Interference Test, TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B, LFT = Letter Fluency Test.

3.6. Language-related Differences in Cognitive Performance

The analysis detected the language-dependent differences in cognitive performance for all cognitive tests under an adjustment for education, gender and language. The evaluations provided by the full models also including language as a predictor was significantly better in terms of the LOO-IC comparisons than the reduced models, which only included age, education and gender as predictors (LOO-IC differences ranged from -162.39 to -32.97, *SE*s = 13.94-28.38, all 95% CIs excluded zero).

The largest data set was obtained from English native speakers was used as a reference for the comparisons between the performance in the neuropsychological tests for other language groups. In this study, the following language groups were examined: English, German, Spanish, Italian, Polish,

French, Danish, Dutch and Latin-American Spanish. All data collected were obtained from the native speakers in the respective language. The mean expected performance on all cognitive tests for each language group and their 95% PPIs are depicted in Figure 27. In addition, all language-dependent differences in the cognitive performance for all cognitive tests are listed in detail in Table 25.

The displayed values represent posterior means and their 95% PPI interval; posteriors values of non-English languages were compared to English as a reference category; consequently, negative values indicate lower scores and positive values indicate higher scores than those obtained in English native speakers.

Despite the low numbers of normal controls for Danish, Dutch, French and Spanish Latin-America (< 50), there were significant differences in several neuropsychological tests in these languages, as shown in Table 25. The study also detected the differences in performance even in the tests considered " language-independent", such as SDMT and TMT-A and B. The Spanish, Italian and Polish native speakers performed worse than French-Canadian and German native speakers, who performed similarly to English native speakers in TMT-A and B. The performance in SDMT in German native speakers was worse than the one observed in English native speakers but better than Polish and Italian native speakers. The differences between native speakers in performance in SDMT, TMT-A and TMT-B remained significant even after adjustment for age and educational levels between the various groups of native speakers. On language-dependent tasks such as the SWRT, there were clear differences between groups of native speakers: Spanish native speakers performed best on the SWRT.

In contrast, Polish native speakers performed worse than all other language groups on all three Stroop subtests. Further, Polish native speakers' performance on CFT and LFT was like that of English native speakers. However, German and Spanish native speakers (and to a lesser extent Italian native speakers) appeared to perform worse on the LFT.

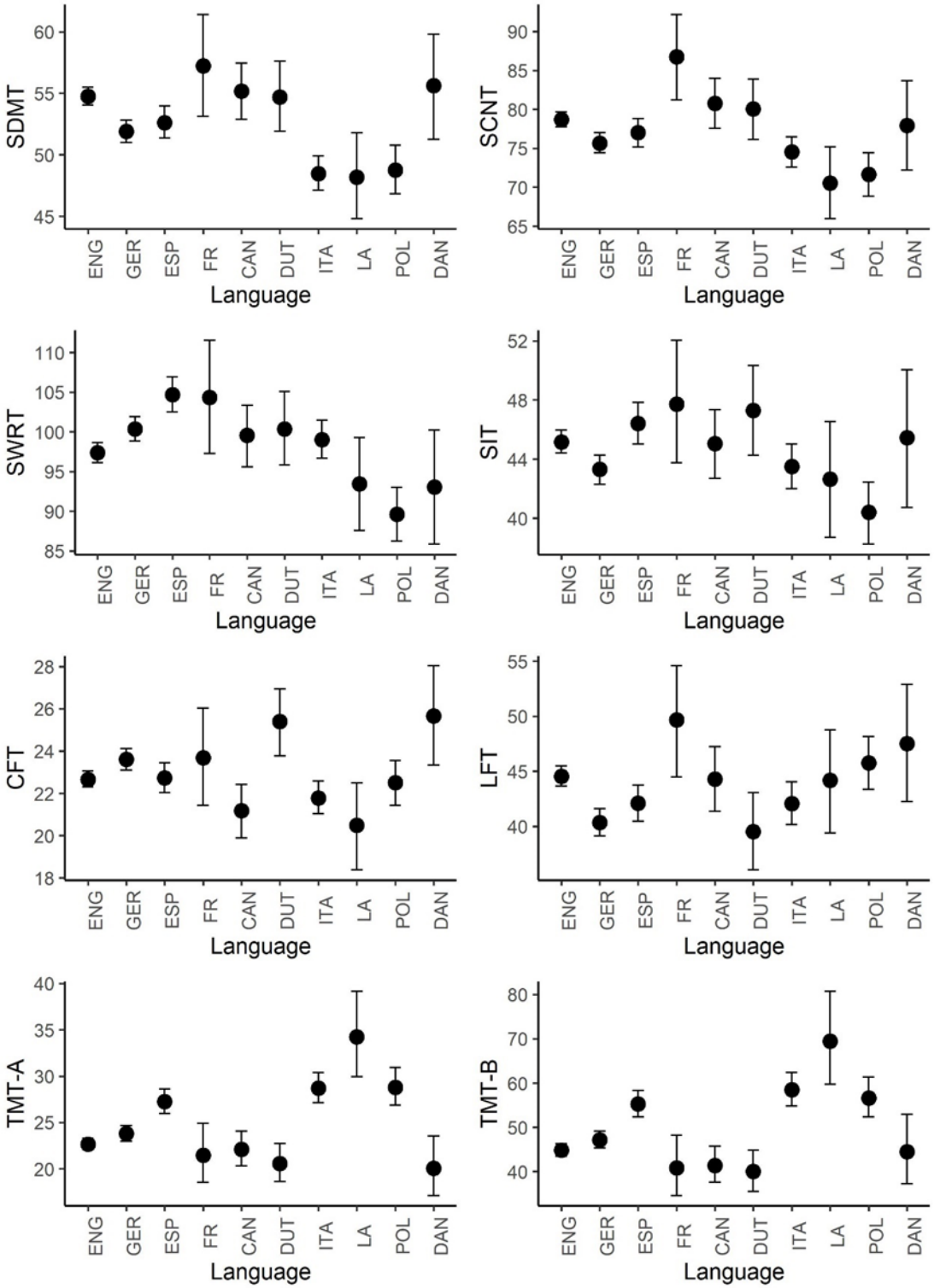


Figure 27: Language differences in tested cognitive measures

Points represent mean estimates of the average performance based on language when age and education are average and female sex; whiskers estimate 95% CIs of the means. It is to note the low numbers of normal controls for Danish, Dutch, French and Spanish Latin-America (< 50). in comparison to data sets from English, German, Spanish, Italian, Polish and French-Canadian language groups

Differences in cognitive performance stratified by language.								
Language	SDMT	CFT	SCNT	SWRT	SIT	TMT-A	TMT-B	LFT
English	0	0	0	0	0	0	0	0
German	-2.86 [-3.77, -2.03]	0.94 [0.45, 1.41]	-3.03 [-4.22, -1.85]	2.95 [1.43, 4.37]	-1.87 [-2.83, -0.96]	0.05 [0.02, 0.08]	0.05 [0.01, 0.09]	-4.19 [-5.37, -3.05]
Spanish	-2.14 [-3.38, -0.88]	0.07 [-0.61, 0.75]	-1.70 [-3.43, 0.02]	7.28 [5.25, 9.39]	1.25 [-0.12, 2.61]	0.18 [0.14, 0.23]	0.21 [0.16, 0.26]	-2.46 [-4.03, -0.88]
French	2.46 [-1.70, 6.59]	1.04 [-1.13, 3.40]	7.97 [2.79, 13.62]	6.97 [-0.12, 14.01]	2.62 [-1.49, 6.85]	-0.05 [-0.20, 0.10]	-0.09 [-0.26, 0.08]	5.09 [0.09, 10.09]
Canadian French	0.39 [-1.87, 2.64]	-1.50 [-2.76, -0.28]	2.06 [-1.16, 5.11]	2.14 [-2.00, 5.69]	-0.13 [-2.43, 2.25]	-0.02 [-0.11, 0.06]	-0.08 [-0.17, 0.02]	-0.29 [-3.27, 2.69]
Dutch	-0.05 [-2.84, 2.85]	2.71 [1.18, 4.33]	1.35 [-2.50, 5.08]	2.97 [-1.91, 7.37]	2.10 [-1.10, 4.89]	-0.10 [-0.20, 0.00]	-0.11 [-0.22, 0.00]	-5.06 [-8.61, -1.61]
Italian	-6.29 [-7.58, -4.90]	-0.88 [-1.65, -0.11]	-4.19 [-6.03, -2.24]	1.64 [-0.64, 3.94]	-1.66 [-3.15, -0.14]	0.24 [0.18, 0.29]	0.27 [0.20, 0.33]	-2.49 [-4.40, -0.62]
Latin America	-6.57 [-9.71, -2.83]	-2.19 [-4.20, -0.13]	-8.15 [-12.93, -3.61]	-3.91 [-9.55, 1.97]	-2.51 [-6.41, 1.36]	0.41 [0.28, 0.54]	0.44 [0.29, 0.59]	-0.38 [-5.14, 4.10]
Polish	-6.00 [-7.97, -4.12]	-0.17 [-1.19, 0.93]	-7.02 [-9.64, -4.03]	-7.80 [-11.03, -4.47]	-4.78 [-6.85, -2.66]	0.24 [0.17, 0.31]	0.23 [0.15, 0.31]	1.21 [-1.13, 3.62]
Danish	0.82 [-3.39, 5.00]	3.00 [0.73, 5.43]	-0.83 [-6.49, 4.91]	-4.38 [-11.30, 3.07]	0.26 [-4.47, 4.77]	-0.12 [-0.29, 0.03]	-0.01 [-0.18, 0.17]	3.01 [-2.25, 8.36]

Table 25: Differences in cognitive performance stratified by language

Values represent posterior means and their 95% Posterior Probability Intervals (PPI, in brackets); posteriors of non-English languages were compared to English as a reference category; consequently, negative values indicate lower score and positive values indicate higher score than the one observed in English speaking participants; cases in bold; PPIs excluding zero are written in bold; TMT-A and TMT-B are presented on a logarithmic scale, all other tests are presented as raw scores. SDMT = Symbol Digit Modalities Test, CFT = Category Fluency Test, SWRT= Stroop Word Reading Test, SCNT = Stroop Color Naming Test, SIT = Stroop Interference Test, TMT-A = Trail Making Test, Part A; TMT-B = Trail Making Test, Part B, LFT = Letter Fluency Test.

3.7. Results Interpretation in Clinical Practice

3.7.1. Illustrative Case Study

The illustrative case study presents a practical example of using normative values. During the study, a 32-year-old female patient, a Polish native speaker living in Germany with known HD, molecularly confirmed with a genetic test giving a result of 18/44 CAG repeats, presented at the clinic to evaluate subjective memory impairment and difficulties in concentration. The patient undertook the whole cognitive battery in the Polish language. She obtained in SWRT a raw value of 77. This value was interpreted by the normative calculator within normal range *z*=-.83 when considering Polish normative values, however in the below-average. When the raw value was evaluated by considering the normative values from other countries (e.g., German) than *z*=-1.52 detected, this indicates a difference in interpretation, referring to the mild cognitive deficit. An overview of the z-scores in different languages is displayed in Figure 28.

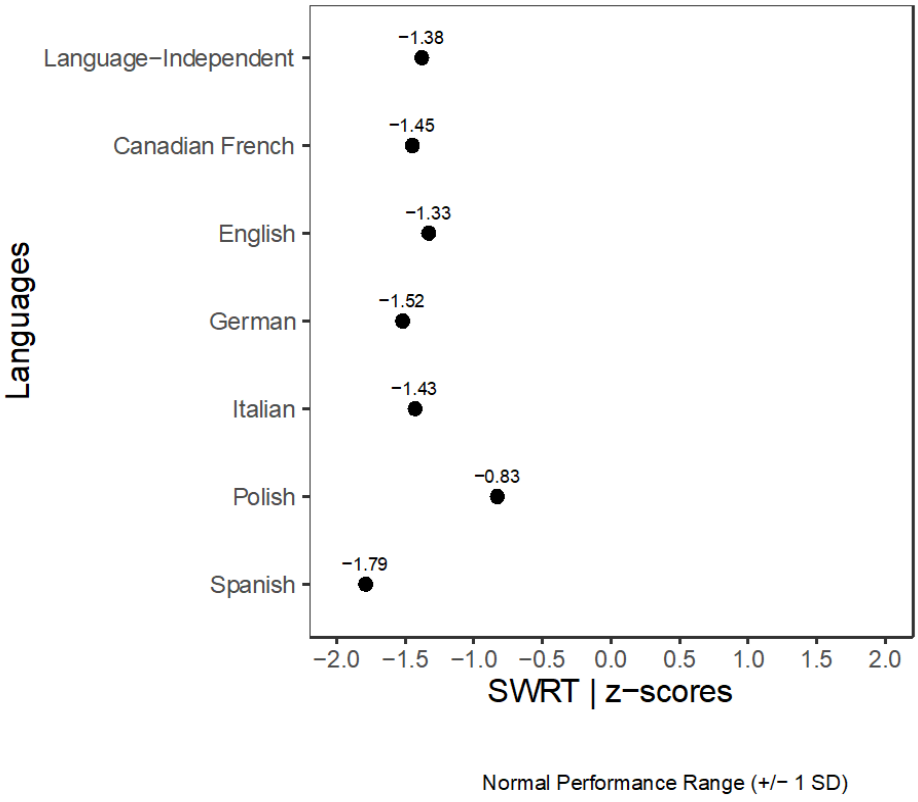


Figure 28: Illustrative Case Study
The figures show a clinical case of a 32-year-old female manifest HD patient, the raw value of 77 in Stroop Word Reading Test (SWRT) language-dependent differences in evaluating performance with different normative values in different languages.

These differences in data interpretation may be partly explained by plain language differences in the patient-facing testing documents. In the SWRT, the words indicating “red", “green”, and “blue” differ in the number of syllables in different languages (e.g., one syllable in English and German and three syllables in Polish, as shown in Table 26. Thus, the number of colour words a proband can read aloud within 45 seconds will be lower in Polish than in languages in which it takes less time to utter these colour words.

Number of syllables in colour words			
Language	Word (Syllables)	Word (Syllables)	Word (Syllables)
English	Green (1)	Red (1)	Blue (1)
German	Grün (1)	Rot (1)	Blau (1)
Polish	Zielony (3)	Czerwony (3)	Niebieski (3)
Italian	Verde (2)	Rosso (2)	Blu (1)
French	Vert (1)	Rouge (1)	Bleu (1)
Dutch	Groen (1)	Rood (1)	Blauw (1)
Spanish	Verde (2)	Rojo (2)	Azul (1)
Danish	Gron (1)	Rod (1)	Bla (1)

Table 26: Language differences for Stroop test concerning the number of syllables in colour words
The table shows the number of syllables in the colour words in the Stroop Word Reading Test in different languages.

Therefore, the performance in the Stroop tests may be misinterpreted as below average or in pathological range if compared to a healthy control population from other languages using monosyllabic words to name colours. However, this study shows that this performance will be evaluated as an average range using the language-specific normative values adapted for the Polish language. The comparison between *z*-scores in SWRT in different languages, as already mentioned, is presented in Figure 28.

A practical illustration of the patient-facing test material, namely the SWRT assessment in English and Polish, is presented in Figure 29.

ENROLL-HD
STROOP WORD READING

Participant ☐☐☐-☐☐☐-☐☐☐ **Date** (MM.DD.YYYY) ☐☐.☐☐.☐☐☐☐

All items must be completed. Use U if information is unavailable. Use N if information is not applicable.

Stimulus Word Reading

RED	GREEN	BLUE	GREEN	RED	BLUE	BLUE	GREEN	RED	GREEN
RED	BLUE	GREEN	RED	BLUE	RED	GREEN	GREEN	BLUE	BLUE
RED	BLUE	GREEN	BLUE	RED	GREEN	RED	BLUE	GREEN	RED
RED	GREEN	BLUE	RED	GREEN	RED	BLUE	GREEN	RED	GREEN
GREEN	RED	BLUE	GREEN	BLUE	GREEN	RED	BLUE	BLUE	RED
RED	GREEN	BLUE	GREEN	RED	GREEN	BLUE	RED	BLUE	GREEN
BLUE	GREEN	BLUE	RED	BLUE	RED	GREEN	BLUE	RED	GREEN
GREEN	RED	BLUE	RED	GREEN	BLUE	RED	RED	GREEN	BLUE
BLUE	RED	BLUE	GREEN	RED	BLUE	GREEN	RED	BLUE	RED
GREEN	BLUE	GREEN	BLUE	RED	GREEN	RED	BLUE	GREEN	RED
BLUE	RED	BLUE	GREEN	RED	BLUE	GREEN	RED	BLUE	RED

ENROLL-HD
TEST CZYTANIA SŁÓW STROOPA

Pseudonim ☐☐☐-☐☐☐-☐☐☐ **Data** (DD.MM.RRRR) ☐☐.☐☐.☐☐☐☐

Proszę uzupełnić wszystkie pola! Proszę wpisać U gdy nie można uzyskać danych; N gdy pytanie nie ma zastosowania

Bodźce do czytania słów

CZERWONY	ZIELONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	NIEBIESKI	ZIELONY	CZERWONY	ZIELONY
CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	CZERWONY	ZIELONY	ZIELONY	NIEBIESKI	NIEBIESKI
CZERWONY	NIEBIESKI	ZIELONY	NIEBIESKI	CZERWONY	ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY
CZERWONY	ZIELONY	NIEBIESKI	CZERWONY	ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	ZIELONY
ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	NIEBIESKI	CZERWONY
CZERWONY	ZIELONY	NIEBIESKI	ZIELONY	CZERWONY	ZIELONY	NIEBIESKI	CZERWONY	NIEBIESKI	ZIELONY
NIEBIESKI	ZIELONY	NIEBIESKI	CZERWONY	NIEBIESKI	CZERWONY	ZIELONY	NIEBIESKI	CZERWONY	ZIELONY
ZIELONY	CZERWONY	NIEBIESKI	CZERWONY	ZIELONY	NIEBIESKI	CZERWONY	CZERWONY	ZIELONY	NIEBIESKI
NIEBIESKI	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	CZERWONY
ZIELONY	NIEBIESKI	ZIELONY	NIEBIESKI	CZERWONY	ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY
NIEBIESKI	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	ZIELONY	CZERWONY	NIEBIESKI	CZERWONY

Enroll-HD, Polish translation, July 20, 2017. Source: enroll-stroop-word-us-1.9

Figure 29: Illustration of language differences between Polish and English in Stroop Word Reading Test patient-facing test materials

3.7.2. Comparison of the Regression-based *z*-scores and Raw Values in the Longitudinal Performance

It is a key point for the research, clinical practice and cares to de-noise data on the cognitive performance of the *htt* expansion mutation carriers. It is particularly impactful in the premanifest or prodromal stages of HD with normal biological decline, not reflecting HD-associated neurodegeneration, which needs to be separated from a decline in excess. From the practical point of view, this study paradigmatically shows on the example of SDMT that regression-based *z*-scores allow better interpretation than raw scores for clinical practice and research of the disease-associated cognitive decline of an older *htt* expansion mutation carrier far from the predicted onset as shown in Figure 30. This illustration presents a healthy control subject (blue), a premanifest *htt* expansion mutation carrier (red) and a manifest HD patient (green) with comparable socio-demographic characteristics.

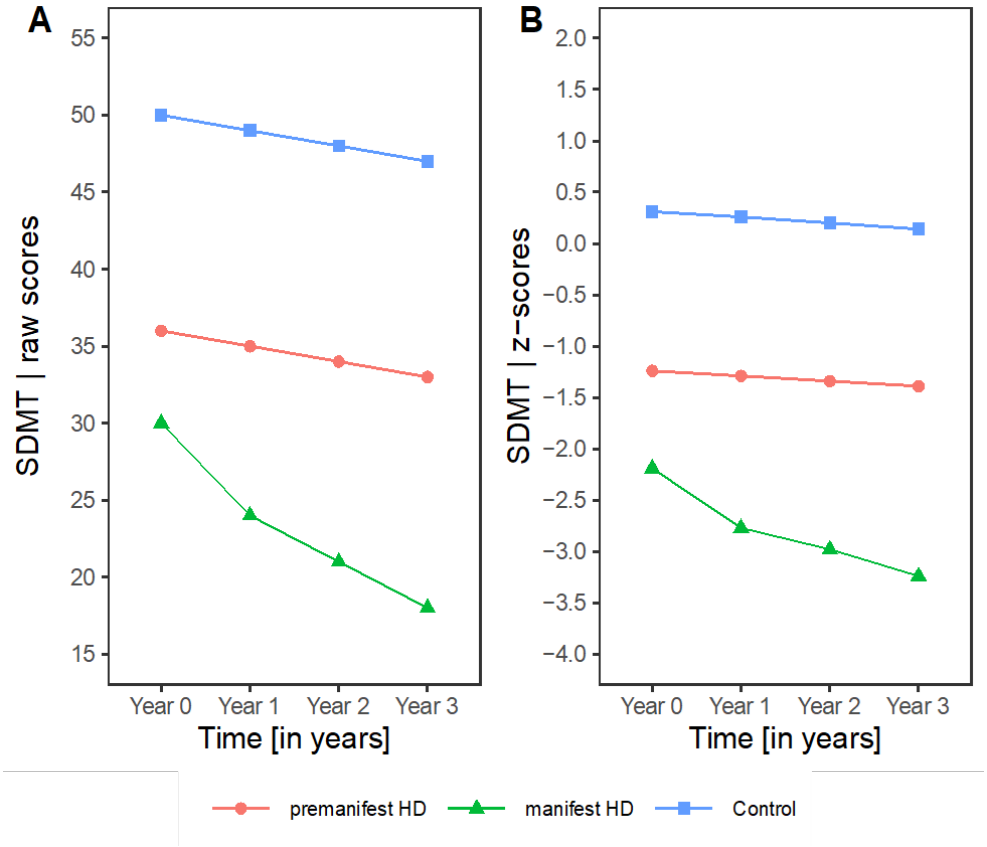


Figure 30: The illustration of the regression-based z-scores on the example of SDMT
This illustration of the regression-based z-scores (part B) allows better interpretation than raw scores (part A) in SDMT on disease-associated cognitive decline of an older HD expansion mutation carrier far from the predicted onset. Raw scores show a decline, z-scores show a straight line. All three subjects were assessed annually over a four-year-period at comparable years of age (blue/control: 60-63 years; red/premanifest HD: 64-68 years; green/manifest HD: 63-66 years), had ≥ 12 years of formal education and were female US-English native speakers. The Points represent z-standardized SDMT performance of the same individuals to allow detection of disease-specific cognitive decline. SDMT = Symbol Digit Modalities Test.

4. Discussion

This study provides normative data for a cognitive test battery to assess patients affected by HD or other primary or secondary neurodegenerative disorders (e.g., FTD, MS, PD, PSP), based on a dataset of *N*=3,267 healthy controls. The study looked at the several confounding factors impacting performance in the respective cognitive tests in healthy controls, including age, level of education and gender. It demonstrated that the language in which the neuropsychological tests are administered systematically influences performance. Therefore, the raw values obtained from the neuropsychological test need to be converted to the z-scores to reduce the impact of the confounders, as mentioned above. In the final step to consider disease-associated alterations at a single patient level and for each assessment, a web-based normative calculator was designed to enable this functioning. This normative calculator is freely accessible to any clinician or researcher to improve clinical care and evaluation of the neuropsychological tests.

Employing neuropsychological tests in clinical practice or clinical studies provide an added value if scores can be interpreted in a meaningful and appropriate way (Strauss et al., 2006). To this end, a participant's score is compared to scores derived from a healthy control population with comparable matched characteristics (e.g., gender, age, education level, language) by applying normative values for diagnostic purposes. In addition, normative values may allow continuous monitoring of the disease's natural progression and may help demonstrate the potential benefits and side effects of clinical interventions of different kinds. Applying the standardized performance scores controlled for the influence of identified confounding factors instead of raw values helps define and quantify the actual, i.e. disease-associated alterations in cognitive performance.

4.1. The Investigated Cognitive Battery

The cognitive battery examined in this study includes the SDMT (Smith, 1982), the Stroop Tests consisting of the SWRT, SCNT and SIT (Stroop, 1935, Golden, 1978) as well as the TMT-A und TMT-B (Section, 1944, Reitan, 1955), the LFT (Benton and Hamsher, 1976) and CFT (Benton and Hamsher, 1976). This battery was put together to identify and cover the cognitive impairment occurring within the six neurocognitive domains based on the classification of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5), including learning and memory, executive function, complex attention, language, social cognition and perceptual-motor function (American Psychiatric Association, 2013). No normative data concerning the cofounding factors for this particular cognitive battery have been so far established. There are only several original publications of the respective tests providing scattered normative data published, however, restricted to a few languages (Scarpina and Tagini,

2017). The used cognitive battery is not only a part of the UHRDS for evaluation of HD (Huntington Study Group, 1996), but the same or similar cognitive assessments are used in other primary neurodegenerative conditions, e.g. PD (Jalakas et al., 2019, Statucka and Cohn, 2019, Sanchez-Luengos et al., 2021), FTD (Plutino et al., 2020) and PSP (Plutino et al., 2020), as well as in secondary neurodegenerative conditions like MS (Chiaravalloti and Deluca, 2008, Langdon et al., 2012, Kalb et al., 2018, Middleton et al., 2020).

4.2. Factors Influencing Cognitive Test Performance in a Cohort of Healthy Controls.

This study examined the most essential confounding factors impacting the performance in the cognitive battery consisting of SDMT, SWRT, SCNT, SIT, TMT-A and TMT-B, LCF, VFT. The main findings were as follows:

- the cognitive performance of healthy controls are influenced by sociodemographic characteristics, including age, education level, gender and language;
- cognitive performance on all tests was significantly better with higher educational levels.
- There were language-dependent performance differences on all neuropsychological tests.
- there was a significant decline in cognitive performance with increasing age in most tests (except LFT); and
- Regarding gender differences, there was a trend towards better female performance. However, this was significant only for performance in SDMT.

In the following, the individual cofounding factor will be discussed in more detail in the below paragraphs.

4.2.1. Impact of Education Level

This study confirmed that education rather than age is an impactful factor for performance in all cognitive tests, and higher levels of education were associated with better performance (Fichman et al., 2009, De Azeredo Passos et al., 2015). The course of life-span changes in cognition is affected by education. Among individuals with a low level of education, the best neuropsychological test performance is observed at an older age than among higher-educated subjects (Ardila et al., 2000). Further, looking closer at the individual test, the results align with other recent normative studies that presented the effect of education on cognitive performance on several cognitive tests, including SDMT and Stroop tests, and showed a nonlinear relationship between education and cognitive performance (Wilson et al., 2009, Mills et al., 2020). The education level does vary within populations and needs to

be considered for an appropriate evaluation (Lam et al., 2013). In another perspective, education seems to be one of the best established preventive measures for cognitive decline and dementia, so it is essential to consider the level of education in normative values (Lövdén et al., 2020).

4.2.2. Impact of Age

Additionally, the analysis confirmed that higher age was associated with a decline in performance on most cognitive tests, except LFT. These findings are consistent with several studies confirming a decline in cognitive performance involving processing speed and executive functions with advancing age (Verhaeghen and Salthouse, 1997, Beeri et al., 2006, Krivanek et al., 2021). Moreover, previous studies also showed no age-related decline in LFT performance (Stricks et al., 1998, Beeri et al., 2006, Goral et al., 2007, Kavé and Knafo-Noam, 2015). Despite changes to brain integrity with ageing, some functions such as language processes remain remarkably preserved (Ansado et al., 2013), possibly due to the compensatory brain networks (Harrison et al., 2015). The LFT, as one of the subdomains of verbal fluency, is commonly used in clinical practice and research. LFT is relatively stable during ageing compared to other fluency domains involving semantic fluency (Elgamal et al., 2011, Gonzalez-Burgos et al., 2019). The stability in phonemic fluency performance has been linked with the contribution of other cognitive domains, including more efficient use of ipsilateral language networks (Gonzalez-Burgos et al., 2020) and perhaps involving a greater capacity to recruit contralateral frontoparietal networks(Gonzalez-Burgos et al., 2019). Letter fluency is assumed to rely more on vocabulary knowledge (i.e., crystallized intelligence), implying some protection against age-related decline (Gordon et al., 2018).

4.2.3. Impact of Gender

One of the most cited reviews, performed by Hyde and Linn, observed that only 27% of the considered studies show a significant female advantage in verbal tasks, whereas 7% of studies found a male advantage(Linn and Petersen, 1985). However, the gender differences in verbal fluency performance and strategies are highly controversial. Nevertheless, some studies suggest a slight female advantage, at least for phonemic fluency (Linn and Petersen, 1985, Scheuringer et al., 2017). Strategies for verbal task performance differed between females and males, while only switching but not clustering was related to overall performance in all verbal fluency tasks. This relationship was dominated by females in the phonemic task but by males in the semantic task (Scheuringer et al., 2017). There is evidence that women switch more often between categories, whereas men generate broader clusters than women (Lanting et al., 2009). Although, the study observed a slight trend towards better performance in females, most marked in SDMT (Jorm et al., 2004, Kiely et al., 2014). In the recent study of Fellow et al., gender was only a significant predictor for SDMT in the written application, with women

performing better, assuming that future studies examining the test application method are needed (Fellows and Schmitter-Edgecombe, 2020).

In summary, the findings on the impact of the SDMT are incontinent, with more evidence toward the female gender (Fellows and Schmitter-Edgecombe, 2020). In line with previous normative studies, the study identified that performance in the Stroop tests (Bezdicek et al., 2015) and verbal fluency measures less influenced by gender (Tombaugh et al., 1999).

4.2.4. Impact of Language

A new finding of this normative study is the influence of the language in which the tests are administered on the cognitive performance of healthy control subjects. However, the same observation has been already described in several, showing the essential impact of language on performance in neuropsychological tests (Bezdicek et al., 2015, Ardila, 2020) and the cultural background (Fernández and Marcopulos, 2008). This study emphasizes the need to address cultural and language biases on cognitive testing (Statucka and Cohn, 2019). The strategies for developing culture - and language-independent cognitive tests that avoid verbal tasks have proven unsuccessful in clinical practice and research (Marcinkowska, 2017, Fernández and Abe, 2018). In the old fashion, it was mostly TMT, and SDMT was considered language-independent, but there is clear evidence that avoiding the verbal task is insufficient. Numerous studies, mostly from Asian regions, evaluated the TMT- part A using other languages than English (Stanczak et al., 2001, Bhatia et al., 2007, Kim et al., 2014), reported that healthy Asians performed worse than English native controls. Such factors could lead to diagnostic errors while evaluating cognitively impaired individuals in different cultural and language contexts. The TMT-B is even more restrained to be used in the different language contexts. Although the TMT may be measuring visual scanning, psychomotor speed and mental flexibility, that are not defined primarily by language, normative data comparison study from ten different countries such as Argentinian, Belgium, Canada, China, Denmark, Italy, New Zealand, Sweden, UK and USA showed that the normative data is not equivalent which might lead to serious diagnostic errors (Fernández and Marcopulos, 2008), although matched for the age and education. In addition, we obtained the same results as the study of Bezdicek et al. showing, TMT-A and TMT-B performance may be significantly faster in Czech and English populations than in Spaniards, demonstrating a lack of sociocultural equivalence on TMT-A and B, suggesting the need for adjustment of available TMT norms for use in different cultures (Bezdicek et al., 2016).

Language and cultural differences have also influenced SDMT performance, even involving adjustment to the basic sociodemographic factors (González et al., 2007, Agranovich et al., 2011, Cores et al., 2015). Different hypotheses are trying to explain the differences in the performance of these tests. For example, a matched sample of Russian and American adults found that cultural differences in time

attitudes were associated with differences in performance on timed neuropsychological tests, including the SDMT (Agranovich et al., 2011). Not all studies comparing different language groups and backgrounds may explain the apparent differences in SDMT by sociodemographic factors (Cores et al., 2015). Indeed, it is now well recognized that ethnicity and, more broadly, culture influence neuropsychological test performance, including psychomotor speed (Fernández and Marcopulos, 2008, Ojeda et al., 2016a, Fernández and Abe, 2018).

Even the Stroop Tests are dependent on the language, as shown in the several studies that established their specific normative values to evaluate Stroop tests appropriately in different languages (Van der Elst et al., 2006).

It is an open question how language influences neuropsychological tests and our performance. Recently, Amici et al. observed that even language syntax might influence verbal working memory. Moreover, speakers of right-branching languages such as Italian (the head of the sentence usually comes first, followed by information modifiers) could process information incrementally (Amici et al., 2019). Another example is the study by Steenhuis and Ostbye, reporting a significant difference in verbal fluency between French and English for the letters F, A and S and Animal Naming (Steenhuis and Østbye, 1995, Ardila, 2020). The language was found to affect verbal working memory, thus potentially explaining an impact on neuropsychological test performance (Amici et al., 2019). There is an obvious need to provide language-specific normative data for appropriate test interpretation from a clinical and research perspective. There is clear evidence for the language-specific norms, as presented in several studies of the Hispanic population living in the English-speaking environment (Ardila et al., 1999, Fortuny et al., 2005, Gasquoine et al., 2007). The strategies to develop culturally and linguistically independent cognitive tests that avoid verbal tasks have proven unsuccessful (Marcinkowska, 2017, Fernández and Abe, 2018).

Although the demographic variables impact neuropsychological scores, few studies examine the relationship between language and cultural background and cognitive scores in patient populations. However, this information is critical because it is vital to consider language when interpreting patient scores (Boone et al., 2007), (Marcopulos et al., 1997, Manly et al., 1998, Manly et al., 2002, Lucas et al., 2005, Ojeda et al., 2016b). These findings are also relevant for multi-centre studies when the same neuropsychological tests are applied in different countries and languages (Katz, 2020). It is also essential to look at the impact of language when considering the generalizability of normative values derived from datasets originating from different countries or cultures (Marcopulos et al., 1997, Manly et al., 1998, Manly et al., 2002, Lucas et al., 2005, Ojeda et al., 2016b, Agelink Van Rentergem et al., 2020).

4.3. Application to Huntington Disease

Although in HD, the clinical diagnosis of HD is typically based on the onset of characteristic motor signs combined with a positive family history, the cognitive impairments stay a key symptom occurring at very early, even premanifest diseases stage (Paulsen and Long, 2014, Paulsen et al., 2017). There is strong evidence from the numerous studies referring to the subtle cognitive deficits in attention, working memory, processing speed, psychomotor functions, episodic memory, emotion processing, perception and executive functions occurring before the diagnostic motor signs, therefore assessing cognitive performance continuously is of high importance for monitoring disease progression (Kirkwood et al., 2000, Paulsen et al., 2008, Snowden, 2017). Several studies have highlighted the importance of monitoring the longitudinally cognitive decline in carriers of the *htt*-expansion mutation at early stages of the disease process (clinically 'premanifest HD') in determining the progression of the disease (Tabrizi et al., 2013b, Paulsen et al., 2014a, Julayanont et al., 2020). As mild cognitive impairment (MCI) is thought to be common in early motor-manifest HD and likely to be a feature even in premanifest HD, normative values will assist in the clinical interpretation of cognitive deterioration, defining cut-off values for MCI (Julayanont et al., 2020).

To track the disease progression longitudinally, a reliable progression marker is needed. Numerous studies established (1) that performance decline in tests assessing psychomotor speed is an early, well-reproduced feature of HD (Stout et al., 2012, Tabrizi et al., 2012, Paulsen et al., 2014a) and (2) that performance decline in the neuropsychological tests in general is – along with an increased motor impairment - a consistent, quantifiable hallmark of disease progression in HD (Roos, 2010, Snowden, 2017). Therefore, performance in SDMT was incorporated – along with the Total Motor Score (TMS) of the UHDRS (Huntington Study Group, 1996) and the Total Functional Capacity (TFC) (Huntington Study Group, 1996) – as a component into a composite score of the UHDRS (cUHDRS) proposed as a potential indicator of the rate of progression in HD (Schobel et al., 2017). However, several confounding factors complicate the interpretation of a decline in cognitive performance score in HD patients, the most important being a decline in performance resulting from normal ageing. Therefore, this study plans to examine the cUHDRS score under consideration of the specific norms established by using the normative calculator.

4.4. Strengths and Limitations

This study was performed on the overall large sample of control subjects with a methodologically beneficial design prospectively and systematically. The cognitive assessments were obtained from bona fide 'healthy' subjects. The participants were prospectively screened for comorbid conditions; the

medical history was annually updated data on the neurological and psychopathological phenotype and ongoing pharmacotherapy and nonpharmacological approaches.

Potential limitations of this study might be that the cohort of controls represents a convenience sample of subjects recruited from families affected by HD, recruited through Enroll-HD study centres. Thus, the sample might not represent the diversity of a population. In addition, the burden of living in households impacted by HD may have some bearing on performance in cognitive tests. The sample size for some languages was insufficient to provide language-specific normative values. From our perspective, it would be desirable to substantially expand the normative data collection, as our results show that the language used during the examination influences cognitive performance.

5. Conclusions

In conclusion, this study established normative data for the cognitive battery consisting of SDMT, Stroop tests (SWRT, SCNT, SIT), TMT-A and TMT-B, Letter and Category Fluency tests from an international, sizeable sample of healthy controls, stratified by age, gender, education and language. In addition, this work resulted in the implementation of an easy-to-use, web-based normative calculator freely accessible to clinicians and researchers worldwide. A range of CNS disorders similar to HD is characterized by executive function impairments and reflects the dysfunction of pre-frontal-striatal thalamic circuits (Mega and Cummings, 1994). However, the anatomical sites responsible for the pathological alterations differ between distinct disease entities, e.g. cortex in frontotemporal dementia (FTD) (Burrell et al., 2016) (Plutino et al., 2020), white matter in multiple sclerosis (MS) (Chiaravalloti and Deluca, 2008, Zhang et al., 2016), basal ganglia in HD (Graybiel et al., 1994, Parent et al., 1995, Blumenstock and Dudanova, 2020) and Parkinsonian disorders (PD), e.g. progressive supranuclear palsy (PSP) (Aarsland et al., 2017, Plutino et al., 2020), thalamus in Creutzfeld-Jakob disease (CJD) (Gibson et al., 2018), the alteration of this circuitry and anatomical structures typically results in similar cognitive impairments.

Based on this fact, the cognitive battery examined in this study may be applied on the principle of the generality to assess the cognitive disruptions referring to the pre-frontal-striatal-thalamic circuits (Albin et al., 1989, Parent et al., 1995, Peters et al., 2016) altered in disorders mentioned above. In particular, it is important to develop an appropriate tool for tracking disease progression; a battery of cognitive tests is well suited for repeated, longitudinal application (Molinuevo et al., 2017) is commonly used.

Aside from first exposure and practice effects (Bartels et al., 2010, Calamia et al., 2012), isolating the impact of disease progression on cognitive performance is of high importance for clinical practice and

research. In line with this approach is minimizing of the key confounding factors, such as age (Alenius et al., 2019), gender (Weber et al., 2014), an education level (Harrison et al., 2015), language and cultural background (Boone et al., 2007) at a single subject level. However, no comprehensive normative data for the mode of application of these commonly employed cognitive tests are available, primarily because of a lack of data from a large cohort of control subjects. In the context of large, international observational studies on the natural history of HD, data were prospectively collected from a sizable cohort of control subjects not carrying the *htt*-expansion mutation.

5.1. Outlook

The neuropsychological assessment itself reflects a culturally embedded process. Culture permeates all aspects of neuropsychological assessment, from the identification and definition of relevant constructs, the development and construction of tests, the clinical interview and observations, the process of test administration and the interpretation of performance (Ardila 2007a, b). Thus, a central question concerns how we can recognize the influence of culture and language on neuropsychological assessment to address such highly varied issues meaningfully. In this way, it is important to continuously develop the appropriate neuropsychological tests considering the key sociodemographic variables, including language and cultural background, or to provide the specific normative values considering the basic sociodemographic. In addition, there is an urgent need to expand the collection of normative data from healthy controls to increase sample size and to cover additional languages missing in the sampling efforts as currently conducted in the context of the Enroll-HD study.

IV. Summary

1. English Summary

Huntington disease (HD) has a severe and profound impact on affected patients and families. It is a hereditary disease that usually appears in middle age and is characterized by a triad of clinical symptoms, including progressive impairment of motor function, cognition, and behavior. Cognitive deficits commonly occur prior to the onset of neurological symptoms by more than a decade and can thus have a significant negative impact on quality of life.

This dissertation focused on the most widely used neuropsychological test battery for HD: the test battery used in the Enroll-HD study, which includes the Symbol Digit Modalities Test, the Stroop Tests, the Trail Making Test - Part A and B, and as well the Category and Letter Fluency Test.

The aim of the first study was to investigate the diagnostic accuracy of the Enroll-HD cognitive battery. A one-way analysis of variance between groups confirmed that healthy controls performed significantly better than HD patients on all cognitive tests (Games-Howell post-hoc analysis $p < .001$). However, the Color Naming Stroop Test showed the highest discriminative potential. Overall, these results confirm that the Enroll-HD cognitive battery is sufficiently sensitive to differentiate between normal cognitive performance and cognitive deficits at different stages of HD.

The objective of the second study was to provide normative data to assess cognitive decline related to the course of the disease. A further aim was to identify cofounding factors that may influence cognitive performance, such as age, gender, language and cultural background and education level. The analysis was performed on a normative sample, N = 3,267 (60.5% female; mean age M = 46.99 years, SD = 14.61, range 18 to 86 years) of healthy controls supported by medical history and standardized neurological and psychiatric examination. The findings demonstrated a significant nonlinear decline in cognitive performance with increasing age. Cognitive performance in all tests was significantly better in individuals with higher educational level. Besides, language-dependent differences in performance were found in all tests. In terms of gender, there was a trend towards better performance for females, but this was significant only for the Symbol Digit Modalities Test.

For clinical practice and research purposes, a freely available web-based normative calculator was designed with the normative dataset. This tool allows the diagnosis of cognitive deficits in carriers of the HD mutation with high accuracy. The findings of the work demonstrate the importance of early detection and monitoring of cognitive decline, its impact on coping with activities of daily living and its potential importance for future clinical trials.

2. Czech Summary – Souhrn

Huntingtonova nemoc (HN) má závažný dopad pro pacienty a jejich rodiny. Jedná se o fatální dědičné onemocnění, které se obvykle projevuje ve středním věku postupným zhoršováním motorických i kognitivních funkcí a poruchami chování. Různé kognitivní deficity běžně předcházejí o více než deset let nástup neurologických příznaků a mohou tak výrazně negativně ovlivňovat kvalitu života.

Tato disertační práce se zabývala nejpoužívanější neuropsychologickou baterií Enroll-HD, která zahrnuje Test modalit čísel a symbolů (SDMT), Stroopův test, Test cesty, kategoriální a fonemickou verbální fluenci.

Prvním cílem této práce bylo prozkoumat diagnostickou přesnost kognitivní baterie Enroll-HD. Jednosměrná analýza rozptylu mezi skupinami potvrdila, že zdravé kontrolní skupiny dosahovaly ve všech kognitivních testech významně lepších výsledků než pacienti s HN (Gamesova-Howellova post-hoc analýza $p < .001$). Nejvyšší diskriminační potenciál vykazovalo pojmenování barev ve Stroopově testu. Tyto výsledky potvrzují, že kognitivní baterie Enroll-HD je dostatečně senzitivní v diskriminaci normálního kognitivního výkonu a kognitivního deficitu v různých stádiích HN.

Předmětem druhé studie bylo vytvoření normativních dat pro hodnocení poklesu kognitivního výkonu souvisejícího s průběhem onemocnění. Dalším cílem bylo odlišit faktory, které mohou ovlivňovat kognitivní výkon, jako jsou věk, pohlaví, jazykové anebo kulturní rozdíly a úroveň vzdělání. Byla provedena analýza normativního vzorku, N = 3 267 (60,5 % žen; průměrný věk M = 46,99 let (SD = 14,61, rozmezí 18 až 86 let) zdravých kontrol podložených anamnézou a standardizovaným neurologickým a psychiatrickým vyšetřením. Výsledky ukázaly, že s rostoucím věkem došlo k významnému nelineárnímu poklesu kognitivního výkonu. Kognitivní výkon ve všech testech byl významně lepší u osob, které dosáhly vyššího vzdělání. Kromě toho byly ve všech testech zjištěny rozdíly ve výkonnosti závislé na jazyce. Z hlediska pohlaví byl zaznamenán trend k lepšímu výkonu u žen, který byl však významný pouze u Testu modalit čísel a symbolů.

Pro klinickou praxi i pro výzkumné účely byla nakonec vytvořena volně dostupný webový normativní kalkulátor, který využívá data z nomativního souboru. Tento nástroj s vysokou pravděpodobností umožňuje diagnostiku kognitivního deficitu u nositelů mutace pro HN. Výsledky práce mimo ukazují význam časného záchytu a sledování poklesu kognitivních funkcí, jejich vliv na zvládání běžných denních aktivit a potenciální význam při testování experimentální léčby.

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VI. Publications

1. Publications in the Context of this Dissertation

Mühlbäck, A., Frank W., Klempířová O., Bezdíček O., Schmitt L., Hofstetter N., Klempíř J. (2020). Validation study of the German Enroll HD cognitive battery: Relationship between cognitive performance, functional decline and genetic load, Disease: Relationship Between Cognitive Performance, Functional Decline, and Disease Burden. Archives of Clinical Neuropsychology, 36(1), 74-86. doi:10.1093/arclin/acaa038. IF: 2,2.

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Hubčíková, K., Rakús, T., **Mühlbäck, A.**, Benetin, J., Bruncvik, L., Petrášová, Z., Brunovský, M. (2022). Psychosocial Impact of Huntington's Disease and Incentives to Improve Care for Affected Families in the Underserved Region of the Slovak Republic. Journal of Personalized Medicine, 12(12), 1941. https://doi.org/10.3390/jpm12121941 IF 4,4

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Reilmann R., Landwehrmeyer. G. B., **Mühlbäck A.**; Bohlen, S. (2022). Huntington-Krankheit kompakt. 1st ed., Stuttgart: Georg Thieme Verlag KG (Germany), 2022, 88 pages (German). ISBN 9783132439047

2. Publications Covering Broader Aspects of Huntington Disease and Movement Disorders

Spieler D., Velayos-Baeza, A., **Mühlbäck, A.**, Castrop, F., Maegerlein, C., Slotta-Huspenina, J., Bader B., Haslinger B., Danek, A. (2020). Identification of two compound heterozygous VPS13A large deletions in chorea-acanthocytosis only by protein and quantitative DNA analysis. Molecular Genetics & Genomic Medicine. doi:10.1002/mgg3.1179. IF: 2,1.

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Van Lonkhuizen, P. J. C., Vegt, N. J. H., Meijer, E., van Duijn, E., de Bot, S. T., Klempíř, J., Frank, W.;Landwehrmeyer, G. B.; **Mühlbäck, A.**; Hoblyn, J.; Squitieri, F.; Foley, P.; Heemskerk, A.-W. (2021). Study Protocol for the Development of a European eHealth Platform to Improve Quality of Life in Individuals With Huntington's Disease and Their Partners (HD-eHelp Study): A User-Centered Design Approach. Frontiers in Neurology, 12(1433). doi:10.3389/fneur.2021.719460. IF: 3,6.

Latoszek E., Piechota M., Liszewska E., Hansíková H., Klempíř J, **Mühlbäck A.**, Landwehrmeyer G. B, Kuźnicki J., Czeredys M., Generation of three human iPSC lines from patients with Huntingtons Disease with different CAG lengths and human control iPSC line from a healthy donor, Stem Cell, Research (2022), doi: https://doi.org/10.1016/j.scr.2022.102931 IF:2,2

Frank, W., **Mühlbäck A.**, Lindenberg, K. S., Hoffmann, R., Ludolph, A. C., (2021). Genspezifische Behandlungsansätze bei der Huntington-Krankheit. Psychopharmakotherapie 2021; 28:187–93.: IF: 0,3.

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VII. Appendix

1. List of Tables

2. List of Figures