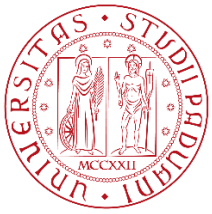

UNIVERSITY OF PADUA

Department of General Psychology

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Multidisciplinary Approach to Phenotypic Variants in Huntington Disease

Final dissertation

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DECLARATION OF AUTHORSHIP

I hereby declare that I have written this thesis titled *"Multidisciplinary Approach to Phenotypic Variants in Huntington Disease"* independently under the professional supervision of *Prof. Roberta Biundo* and *Dr. Michela Garon*, and that I have not used any resources or tools other than those specified.

In Padua, 31.10.2024 _____

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ABSTRACT

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Huntington disease (HD) is a rare neurodegenerative disorder with an autosomal dominant inheritance pattern, caused by an abnormal expansion of trinucleotide cytosine-adenine-guanine (CAG) repeat in the huntingtin gene. This mutation leads to neural degeneration within the basal ganglia, particularly targeting striatum, resulting in a spectrum of motor, cognitive, and psychiatric symptoms. The first aim of this study was to explore variations across different HD stages. The second was to investigate differences among HD phenotypes based on clinical presentation at age of onset. Our research population consisted of a total of 45 participants. All participants were included in the first research sample and divided into presymptomatic (n = 4), prodromal (n = 12), and manifest stage (n = 29). Our second research sample comprised 39 participants, categorized by initial symptoms, either with (Motor +, n = 13) or without (Motor -, n = 26) motor manifestations. All data were collected from comprehensive neurological, neuropsychological, and neuroradiological assessments conducted at Padua University Hospital between 2012 and 2024. Statistical analyses were performed using R (version 4.4.1), with voxel-based morphometry used for neuroimaging data. Our results showed stastistically significant progression in motor, cognitive, and functional capacities, though no statistically significant differences were found for behavioral symptoms. Additionally, the group with initial motor manifestations showed significantly greater motor impairment, while patients without motor onset demonstrated higher functional independence. These findings suggest that motor symptoms have a greater impact on functional capacity than neuropsychiatric symptoms. Notably, attention and social cognition appeared sensitive in distinguishing between presymptomatic and prodromal stages, though further investigation is necessary.

Key words: Huntington disease, phenotypic variants, diagnosis, clinical symptoms

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1 INTRODUCTION

"It is spoken of by those in whose veins the seeds
of the disease are known to exist, with a kind of horror,
and not at all alluded to except through dire necessity,
when it is mentioned as "that disorder"."
GEORGE HUNTINGTON, *On Chorea* (1872)

Rare disorders are generally neglected by the scientific community for various reasons, such as low prevalence often combined with high complexity. However, this does not make them any less relevant compared to more common diseases. Neurodegenerative diseases are no exemption to this issue, which inspired us to focus on Huntington disease (HD), a rare autosomal dominant disorder affecting the central nervous system (World Health Organization, 2022). It is caused by an abnormal cytosine-adenine-guanine (CAG) trinucleoide repeated in the Huntigtin gene (HTT) (Caron et al., 2020), which leads to neuronal death in the basal ganglia, particularly in the striatum. Clinically, this manifests as a set of motor, cognitive, and psychiatric symptoms that progressively worsen over time (Nopoulos, 2016). However, the clinical presentation of HD can vary significantly between patients, even among those with the same CAG repeat lenght, including members of the same family (Roth, 2019; Wexler, 2012). Consequently, we decided to investigate different phenotypic variants in HD based on their initial clinical presentation at the age of onset. More specifically, we aimed to examine the development of clinical profiles (motor, cognitive, and psychiatric/behavioral symptoms) in patients with distinct HD phenotypes,, as well as already established inter-stage differences.

The first chapter of this thesis is dedicated to a comprehensive theoretical background, including previous scientific observations on differences across HD stages as well as phenotypic heterogenity in HD, which served as a basis for formulating our research aims. The second chapter describes the overall methodology used in our research, including our research aims and research questions; definitions of variables; characteristics of participants; and our approach to data collection and analysis. In the third chapter, we present the main results, providing answers to our research questions. These findings are then interpreted in the fourth chapter, where we also discussed the practical implications, limitations, and future directions of this research. Finally, the last chapter offers an overall summary of our work and our findings.

1.1 History and definition of Huntington disease

HD has a remarkable **historical context**, and its clinical description has been refined by different professionals from all around the world throughout the past few centuries. Hence, before analyzing various medical aspects of this disease in more depth, it seems necessary to begin with discussing its initial delineations (Harper, 2002).

The name of the HD is currently attributed to the American physican George Huntington, who was the first to provide a detailed description of what he called "Hereditary Chorea" (Stevens, 1972). According to the National Institute of Neurological Disorders and Stroke (NINDS, 2023), ***chorea*** can be defined as a movement disorder characterized by abrupt, irregular and spontaneous jerky movements of the limbs and facial muscles, similarly to what is observed in patients with HD.

The term chorea originally derives from the Greek "koreia" and/or Latin "choreus" which can be translated as "dance" (Stevens, 1972; Wild & Tabrizi, 2007). Its first medical reference dates to the early 16th century, when the Swiss alchemist Paracelsus used the expression "Chorea Sancti Viti" or ***"Saint Vitus'dance"*** to describe an ongoing epidemic of chorea in Europe, also called "dancing mania" (Vale & Cardoso, 2015; Wild & Tabrizi, 2007). Later on, the English clinician Thomas Sydenham noticed the presence of this disease in children which thereafter became known as ***"Sydenham's chorea"*** (Vale & Cardoso, 2015).

The heritability of this condition started to be emphasized at the turn of the 18th and 19th centuries, subsequently leading to preliminary descriptions of ***adult hereditary chorea***. An instance of this was identified within the medical record of the English practitioner John Elliotson (1832), who has made several observations. First of all, he noted that altough St. Vitus' dance typically had childhood onset, this condition could affect adults as well. Second of all, when present in adulthood, it was usually accompanied by cognitive impairment, and it was most likely impossible to treat. Lastly, he pointed out that this disease often occurs throughout the generations, therefore having a hereditary nature (Stevens, 1972).

However, it might seem that in his documentation, Elliotson described what we now call HD, the first official mention is considered to be the one by American physician Charles Oscar Waters (1841), whose paper was later published in *The Practice of Medicine* (Harper, 2002). In his letter, Waters accurately illustrated chronic adult chorea, which he referred to as "magrums", meaning "fidgets" in Dutch (Stevens, 1972; Vale & Cardoso,

2015). Furthermore, he put a particular emphasis on the adult onset with gradual progression of motor and cognitive symptoms, as well as inheritance of this disease (Bissonnette et al., 2019; Vale & Cardoso, 2015).

Independent of Waters, a Norwegian physician Johan Christian Lund provided a description of this condition in 1860 (Harper, 2002). Lund noticed an increasing prevalence of neurocognitive disorder associated with movement disorders, particularly with symptoms of involuntary twitches, in the Setesdal valley in Southern Norway. He described presence of these jerky movements in the medical reports of two families which supported the idea about the heritability of this disease (Bissonnette et al., 2019). Unfortunately, Lund's work remained unrecognized for an entire century, mainly because it was writen in Norwegian and simultaneously due to the fact that later reviewers assigned his description to Parkinson's disease (Harper, 2002).

Another separate account was documented by the American physician Irving Whitall Lyon in 1863. In his article "Chronic Hereditary Chorea", Lyon described a type of chronic chorea with a peculiar origin, manifested as irregular muscle action. In one of three observed families, he noticed the occurance of this disease across five consecutive generations, therefore emphasizing its hereditary transmission (De Jong, 1937). Additionally, Lyon's paper is commonly regarded as the first to depict the presence of HD in childhood. However, the combination of early onset and the absence of progression suggests that his description aligns better with benign familial chorea[1] rather than HD (Harper, 2002).

As already mentioned, the most prominent figure associated with HD is undoubtedly George Huntington, who made a major contribution to the discovery of this, as he called it, "medical curiosity" (Wexler et al., 2016). Huntington wrote his famous report "On Chorea" (1871), which was later published in *The Medical and Surgical Reporter* (1872). As the title suggests, this paper was discussing the concept of chorea, however, the last part of it was dedicated to the presentation of hereditary chorea which is considered to be the most detailed description up to that point (Harper, 2002). According to George Huntington (1872), chorea is a rare disease of nervous system which is commonly manifested as "dancing popensities". The most distinct feature of this condition is considered to be clonic spasms of the voluntary muscles resulting in persistent jerky movements. Hereditary chorea exhibits all the symptoms of ordinary chorea, albeit with

[1] Benign familial (hereditary) chorea is a non-progressive hyperkinetic movement disorder with the onset in early childhood (Peall & Kurian, 2015).

increased severity, hereditary nature, solely adult onset and suicidal ideations or attempts (Huntington, 1972).

The appreciation of Huntington's subsequent workers led to the further popularization of his renowned paper. One of these supporters was William Osler, who was interested in researching different types of chorea and designated Huntington's paper as one of the most remarkable in the history of medicine (Browning, 1908; Harper, 2002). A few years later, in 1887, a Swiss physican Armin Huber was the first to refer to this condition as ***"Huntington's chorea"*** (De Jong, 1937). Finally, in the late 1960s, the name of Huntington chorea was changed to ***"Huntington disease"*** and has remained so up to this point (Wexler et al., 2016).

Historical observations of HD and its heritable features have naturally strived the motivation to examine its genomics more broadly (Wexler et al., 2016). The first successful attempt to identify HD gene is dated back to 1993, when Nancy Wexler and her team (The Huntington's Disease Collaborative Research Group [HDCRG]) conducted their famous Venezuela project. With the initial aim of finding a cure for this disease, the research group conducted analyses on the Venezuelan population, which was known for its high incidence of HD cases. During this experiment, they discovered that gene related to HD is located on chromosome 4p16.3 (HDCRG, 1993; Wexler, 2012).

Gene discovery has become an important milestone in HD research and has contributed to establishing diagnoses for patients with this disease (Kay et al., 2017). Consequently, HD is now **defined** based on the results of genetic testing, which can be supported by the presence of clinical manifestations and positive family history (Roos, 2010; Tabrizi et al., 2021). Advantageously, this approach is useful in not only confirming or rejecting the presence of HD, but also in identifying patients at risk for developing the disease (Caron et al., 2020; Martino et al., 2012; Roos, 2010).

Noteworthy historical background of HD includes contributions of different medical experts from whom George Huntington was the one attributed with the discovery of this disease (De Jong, 1937; Harper, 2002). He precisely described the clinical manifestations of so-called hereditary chorea which explicitely sparked the international interest in its further examination (Harper, 2002). Thus, in order to better understand additional aspects of this disease, the following sub-chapter breaks down its epidemiological concepts.

1.2 Epidemiology

Investigation of the **epidemiological** aspect of HD mainly involves assessing individuals with the abnormal cytosine-adenine-guanine (CAG) repeat sequence. Additionally, clinical manifestations are taken into consideration, as not all individuals with this mutation already exhibite evident disease signs (Kay et al., 2017). Considering the crucial role of genetics in HD, the frequency of this disorder is most effectively examined by analyzing families in which the condition is inherited (Harper, 2002).

Epidemiological studies approximate the global prevalence of HD between 5 to 10 cases per 100,000 individuals while incidence ranges between 1 to 4 cases per 1,000,000 individuals per year (Rojas et al., 2022). The highest prevalence has bbeen reported in populations of European descent, such as Northern American countries, with around 8.87 per 100,000 (Medina et al., 2022), in particular, Canada – around 17.27 per 100,000 and the United States – around 6.52 per 100,000 (Rojas et al., 2022). Moreover, high prevalence rates are observed in Australia – around 8.4 per 100,000 (Layton et al., 2021) and European countries – around 5.16 per 100,000 (Rojas et al., 2022), including the United Kingdom – around 12.3 per 100,000 (Evans et al., 2013), and Italy around 3.9 per 100,000 (Riccò et al., 2020). In contrast, the lowest prevalence has been documented mainly in Asian countries – around 0.42 per 100,000 (Rawlins et al., 2016); and African countries – around 0.25 per 100,000 (Medina, 2022). These substantial disparities among different geographic areas may stem from natural variations in genetic structure, as well as lack of neurological healthcare access, which could potentially lead to underreporting of HD prevalence (Kay et al., 2017; Rawlins et al., 2016).

Overall, the prevalence of HD has been increasing over the time, possibly driven by factors such as longer life expectancy, diminished stigma of diagnosis (Jiang et al., 2023), and the introduction of genetic testing in the early 1990s (Kay et al., 2017). Understanding the genetic basis of HD is nowadays crucial for accurate and precise diagnosis, thus the relevance of etiology and pathogensis will be discussed in the next subchapter.

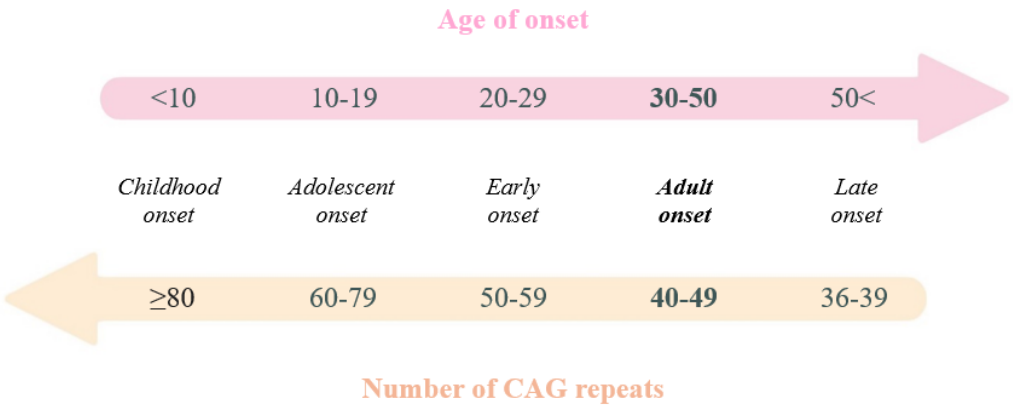
1.3 Etiopathogenesis

As already indicated before, HD is a genetic condition which gets inherited as an autosomal dominant trait. This means that HD gene is not located on neither the X nor on the Y chromosome (Wexler, 2012), and therefore, it affects both male and female genders

equally (Meoni et al., 2020). To be specific, location of the gene corresponding to HD was found close to the telomere of chromosome 4p16.3, which encodes a protein called huntingtin (HTT) (HDCRG, 1993; Wexler, 2012).

The main **etiological** component of HD is the mutation of HTT (mHTT), which is characterized by an abnormally expanded polyglutamine repeat[2] (Tabrizi et al., 2020). The length of this repeat is the most crucial factor determining the age of onset in patients with HD (Wexler, 2012). Healthy individuals predominantly display alleles with less than 26 repeats, and together with the intermediate alleles possessing repeats from 27 to 35, typically do not produce any clinical manifestations (Rojas et al., 2022). Alleles with 36 to 39 repeats tend to show reduced penetrance associated with late onset, usually after the age 50 (Jiang et al., 2023; Tabrizi et al., 2020). The most common age of onset is between 30 and 50 years, with majority of the cases having a number of repeats between 40 and 49 (Nopoulos, 2016; Wexler, 2012). Expansions with 50 and more triplets are associated with early adult onset, typically in a person's 20s, while alleles with more than 59 repeats are common in the adolescent age group (Nopoulos, 2016). Least likely, but not impossible, are repeats larger than 80, which correspond to childhood onset (Jiang et al., 2023; Nopoulos, 2016). Generally, it is possible to observe an inverse relationship between the age of onset and length of the repeat (Nopoulos, 2016). Therefore, in order to better visualize this relationship, we present a following Figure 1.

Figure 1. Correlation between the age of onset and the number of CAG repeats



Note: The expansion of the CAG repeat is shown to be negatively correlated with the initial onset age. Therefore, higher numbers of polyglutamine repeats are associated with earlier age of manifestation, while conversely, the lower the number of repeats, the later the age of onset (Nopoulos, 2016).

[2] HD is also known as a polyglutamine disease (in fact, it is the most common of all polyglutamine diseases). This is because the trinucleotide CAG codes for amino acid called glutamine, therefore its expansion is naturally referred to as "polyglutamine" (Tabrizi et al., 2020, Jiang et al., 2023).

Moving forward, the main **pathological** feature related to HD is an abnormal aggregation of mHTT forming fibrillar structures (Rojas et al., 2022; Ross & Tabrizi, 2011), which due to its toxicity causes neuronal degeneration (Nopoulos, 2016), primarily in basal ganglia (Jiang et al., 2023). Pathophysiology of mHTT is degeneration of pyramidal neurons for example, in cingular gyrus (Nopoulos, 2016), which, according to Jiang et al. (2023) causes mainly mood alterations. On the other hand, degeneration of these pyramidal neurons in the motor cortex causes motor symptoms. Neuroanatomically, this leads to a degeneration of striatal cells, particularly the GABAergic medium spiny neurons of the striatum. These neurons project to the globus pallidus, substantia nigra and thalamus which are involved in two motor pathways – direct and indirect. The first to be affected is the indirect pathway, where striatal neurons project simultaneously to globus pallidus externa and subthalamic nucleus, and then to globus pallidus interna. This pathway is also called the inhibitory pathway and it is responsible for inhibiting involuntary movements. Thus, disruption in this pathway leads to a hyperkinetic state characterized by involuntary (or choreic) movements. Later in the disease, the direct pathway gets affected as well. In this pathway, the neurons are not passing through the globus pallidus externa but rather project directly to the globus pallidus interna. This pathway is responsible for initiating movements and therefore its disruption causes hypokinetic stage, characterized by motor impersistence and akinesia (Jiang et al., 2023).

Broadly, the key pathological characteristic of this disease is the abnormal misfolding of mHTT, resulting in the degeneration of predominantly striatal neurons (Nopoulos, 2016). The main cause of HD is considered to be an expanded CAG repeat (or mHTT), most commonly between 40 and 50 repeats, corresponding to an adult onset (Rojas et al., 2022). This mutation is identified using genetic testing, which plays a crucial role in establishing a correct diagnosis (Caron et al., 2020). Therefore, the next section of this thesis addreses the diagnosis of HD.

1.4 Diagnosis

Nowadays, the **diagnosis** of HD requires a complex assessment of the patient's status, including neurological, cognitive, and psychiatric examinations, as well as molecular evaluation (Caron et al., 2020). Particularly, HD is thought to be present in individuals with a positive genetic test for expanded alleles with at least 36 CAG repeats

(mHTT). Genetic testing is usually requested for patients who have already developed clinical signs and/or symptoms corresponding to HD, or for those with a positive family history of HD (Caron et al., 2020; Reilmann et al., 2014).

Given the fact that HD is primarily a movement disorder, motor symptoms are typically the most prominent ones (Ross et al., 2019). These manifestations are usually assessed using the Diagnostic Confidence Level (DCL), which provides information on the clinician's level of certainty that observed movement symptoms have emerged as a consequence of HD (Tabrizi et al., 2022). According to Hogarth et al. (2005), the DCL is expressed on the scale from *0* to *4*. A score of *0* reflects a normal status, indicating that the patient does not exhibit any movement alterations. A rating of *1* is associated with clinician's confidence of less than 50%, as evident motor symptoms are present, but it is uncertain whether they are due to HD. If a patient displays movement abnormalities that could potentially be signs of HD, the DCL is scored as *2*, corresponding to a confidence level between 50-89%. The movement symptoms that are most likely manifestations of HD are rated as *3* and signify a confidence level of 90-98%. Finally, if the clinician is ≥99% certain that patient's motor abnormalities are unequivocally due to HD, the ultimate DCL score is *4* (Hogarth et al., 2005).

Over the years, there have been several attempts to set **diagnostic categories** for HD (e.g. Reilmann et al., 2014; Ross et al., 2019; Tabrizi et al., 2022). This thesis synthetsizes the main ideas of these different approaches and presents them as follows. The diagnostic categories of HD can be divided into two main periods based on the presence or absence of clinical symptoms: 1) the Preclinical HD, and 2) the Clinical HD (Roos, 2010).

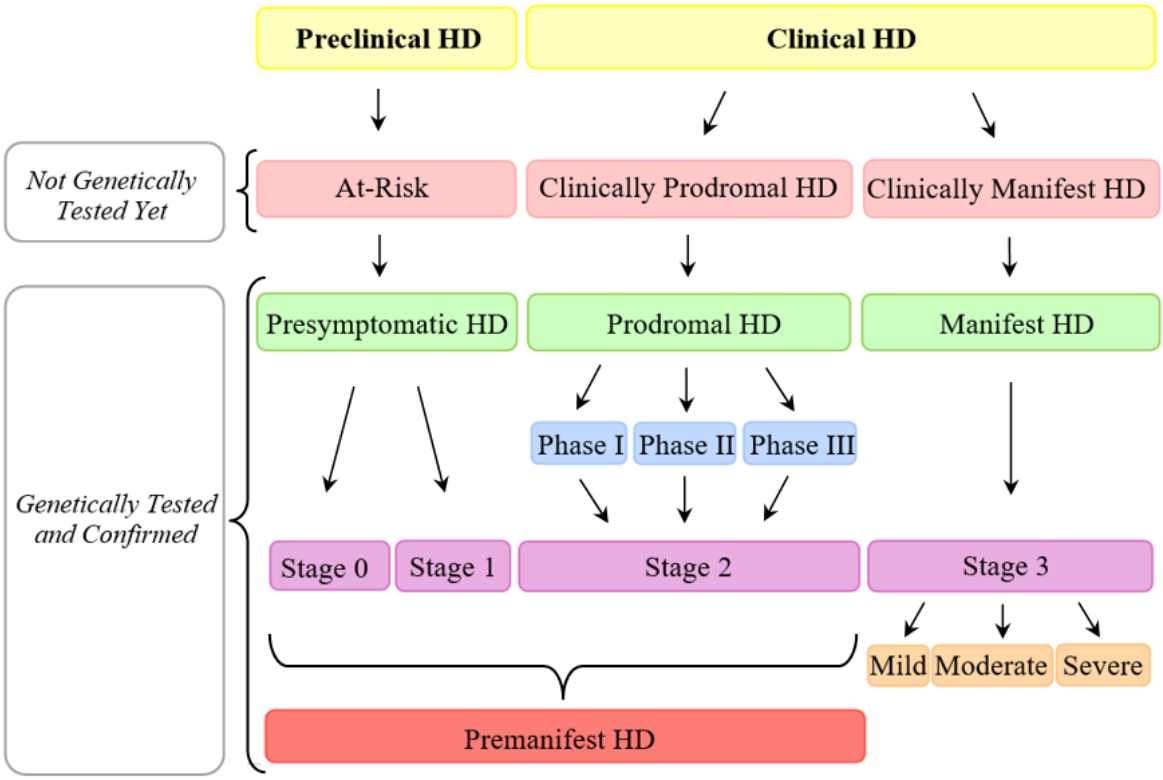
The ***"Preclinical HD"*** is typically characterized by the absence of clinical manifestations, meaning that no symptoms or signs of the disease are present (Roos, 2010). This period includes the initial phase, ***"At-Risk"***, of developing the disease, where those with an affected parent or a parent with positive genetic test can be categorized, even if they have not yet undego genetic testing themselves (Reilmann et al., 2014; Roos, 2010). From the moment a person receives a positive molecular test, they can be considered as having ***"Presymptomatic HD"*** and their DCL score is typically *0* or *1* (Reilmann et al., 2014; Roos, 2010). According to the Integrated Staging System (ISS), this phase starts as ***"Stage 0"*** (Tabrizi et al., 2022), which refers to the time prior to the occurrence of pathological biomarkers, signs/symptoms, or functional decline that could be associated with HD. Thus, this stage begins prenatally and involves the process of neural development accompanied by abnormal expansion of CAG repeat in the gene HTT (Tabrizi et al., 2021).

The first detectable changes are those underlying neural degeneration, also known as biomarkers of pathology, indicating the subsequent ***"Stage 1"*** (Tabrizi et al., 2021; Tabrizi et al., 2022). The major landmark of this stage is the reduced brain volume in the basal ganglia (Rojas, et al., 2022), particularly the atrophy of the caudate and putamen (Tabrizi, et al., 2021).

The period of ***"Clinical HD"*** begins with the onset of the first minor symptoms (Roos, 2010), which can emerge up to 20 years before the full manifestation of the disease (Caron et al., 2020). In former times, the earliest sign of HD was always considered to be a motor symptom. However, it is now clear that cognitive as well as psychiatric symptoms may occur long before the motor onset begins (Roos, 2010). Early motor disturbances with a score of *2* on the DCL and/or subtle cognitive manifestations signalize the start of ***"Prodromal HD"*** (Caron et al., 2020), which corresponds best with ***"Stage 2"*** of ISS (Tabrizi et al., 2022). Furthermore, Rojas et al. (2022) suggest that the onset of cognitive signs before the motor diagnosis can be divided into three main phases. The first phase, ***"Phase I"***, is characterized by aforementioned neuropathology and slight cognitive complications, especially fatigue, which is commonly misinterpreted as a sign of depression or apathy. ***"Phase II"*** is distinguished by the presence of cognitive difficulties, such as impairment in social cognition, memory, attention, processing speed and visuospatial abilities. Along with hyposmia, these symptoms may arise up to 13 years before the diagnosis of motor onset. The last of these phases is ***"Phase III",*** which is closest to the motor diagnosis of HD (within next 7 years). An individual in this phase demonstrates more prominent cognitive impairment of previously mentionted domains, usually accompanied by a lack of insight (Rojas et al., 2022). For patients, who have not undergone genetic testing yet, this timeframe can be defined as ***"Clinically Prodromal HD"*** (Reilmann et al., 2014). Additionally, both presymptomatic HD and prodromal HD can be grouped together as ***"Premanifest HD"***, depicting the period before the final ***"Manifest HD"*** (Ross et al., 2019), or if genetic confirmation is not yet established, as ***"Clinically Manifest HD"*** (Reilmann et al., 2014). Manifest HD is best described based on the presence of cognitive and motor symptoms (with a DCL score of *3* or *4*) that affect functional aspect of person's everyday life (Caron et al., 2020). In the ISS, this definition aligns with the ultimate ***"Stage 3"*** (Tabrizi et al., 2022), which is further delineated according to three functional landmarks. A ***"Mild"*** functional change is attributed to individuals who do not require assisstance with their activities of daily living, but may have some difficulties completing them. If a person needs help with some everyday

activities but is still relatively independent, we refer to ***"Moderate"*** functional decline. Lastly, ***"Severe"*** impairment in everyday functioning can be diagnosed in patients who have completely lost their ability to perform their routine activities and therefore require full assisstance (Tabrizi et al., 2021). Considering this comprehensive summary of all diagnostic categories defined by different professionals, we now provide an overview of these findings in Figure 2.

Figure 2. Overview of different approaches to the diagnosis of HD



*Note: The yellow boxes denote the main diagnostical distinction of HD by Roos (2010) – **Preclinical HD** and **Clinical HD**. The subsequent pink boxes categorize individuals who are "not genetically tested yet" into three groups – **At-Risk**, **Clinically Prodromal HD**, and **Clinically Manifest HD**. These categories correspond to **Presymptomatic HD**, **Prodromal HD**, and **Manifest HD** for genetically confirmed individuals, depicted in the green boxes (Reilmann et al., 2014; Roos, 2010). According to Rojas et al. (2022), **Prodromal HD** can be further divided into three phases – **Phase I**, **Phase II**, and **Phase III**, represented in the blue boxes. The Integrated Staging System by Tabrizi et al. (2022) is outlined in the purple boxes – **Stage 0**, **Stage 1**, **Stage 2**, **Stage 3**, with **Stage 3** subdivided into **Mild**, **Moderate**, and **Severe** based on the severity of functional decline (orange boxes). Finally, Ross et al. (2019) proposed **Premanifest HD**, in the red box, as a category merging **Presymptomatic HD** and **Prodromal HD**.*

In the case of **juvenile HD** (childhood or adolescent onset), clinical manifestations are slightly different from those generally observed in adult patients (Rojas et al., 2022). In particular, the most prominent symptoms are motor-related, specifically hypokinesia and/or bradykinesia with dystonic components (Nopoulos, 2016; Roos, 2010). Psychiatric and

behavioral distubances are also more pronounced in juvenile HD patient with an emphasis on impulsivity, aggressivity, mood dysregulation and hyperactivity (Nopoulos, 2016). Furthermore, cognitive impairment can result in learning difficulties, which, together with the behavioral problems, are usually the first observable signs (Roos, 2010). Moreover, seizures are often present and, due to their severity, might be difficult to treat (Nopoulos, 2016).

Although the clinical diagnosis of HD usually corresponds to the results of genetic testing (90-99%), there is still some probability of misdiagnosis (Cardoso, 2014; Martino et al., 2012). Principally, **differential diagnosis** should be considered in patients who exhibit clincal symptoms of HD, such as abnormal disease progression and/or negative genetic test results (Martino et al., 2012). These individuals are known as HD phenocopies, which can result from various hereditary or non-hereditary conditions (Caron et al., 2020).

Non-hereditary conditions are generally atributed to symptoms of chorea with an acquired cause (e.g. drug-induced, autoimmune/inflammatory diseases) (Caron et al., 2020; Stoker et al., 2022). The most common is tardive dyskinesia (Cardoso, 2014), typically characterized by involuntary movements around the mouth with possible involvement of the trunk and limbs (Stoker et al., 2022). Other non-inherited conditions that may cause symptoms of chorea include thyrotoxicosis, levodopa-induced dyskinesia, cerebrovascular disease, among others (Caron et al., 2020).

Hereditary conditions can be further divided into two groups: autosomal-dominant and autosomal-recessive causes. Among the autosomal-dominant HD phenocopies, the most frequent are Huntignton disease-like 2 (HDL2) and spinocerebellar ataxia 17 (SCA17, otherwise called Huntignton disease-like 4 [HDL4]) (Cardoso, 2014; Martino et al., 2012). HDL2 is clinically impossible to differentiate from HD (Caron et al., 2020) but should be considered in families mainly of Southern African origin (Martino et al., 2012). SCA17 (or HDL4) is similar to HD, manifested by chorea, psychiatric, and neurocognitive disturbances, but its distinguishable feature is cerebellar ataxia (Caron et al, 2020). Additionally, these HD phenocopies may also be caused by spinocerebellar ataxia 1, Huntignton disease-like 1, benign hereditary chorea, dentato-rubro-pallido-luysian atrophy, neuroferritinopathy and many more (Cardoso, 2014). In contrast, the group of autosomal-recessive phenocopies of HD include chorea-acanthocytosis (ChAc), Huntignton disease-like 3, Friedreich's ataxia, Wilson's disease, McLeod's syndrome, ataxia with oculomotor apraxia, and so on (Cardoso, 2014; Stoker et al., 2022). ChAc is the most common of these

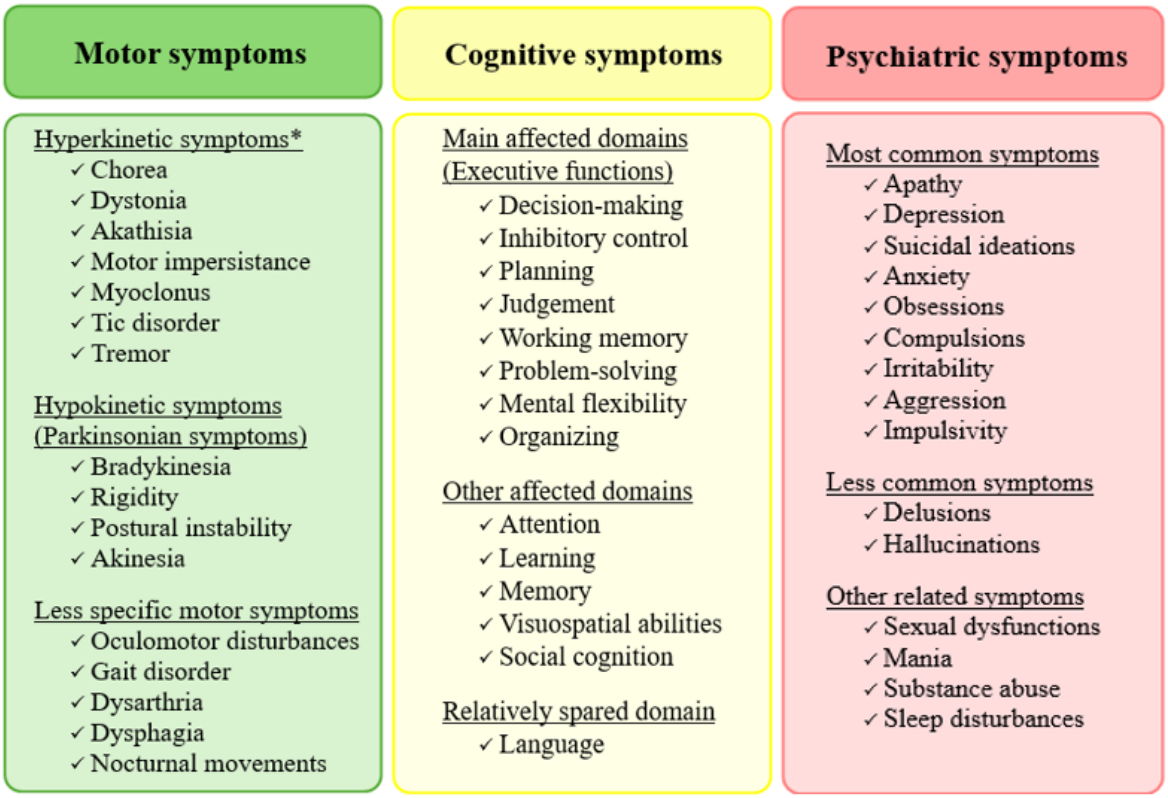
diseases and is differentiated from HD by the presence of myopathy, often seizures and a mean age of onset around 30 years (Cardoso, 2014; Caron et al., 2020).

Comprehensively, the diagnosis of HD is based on the positive results for mHTT on genetic testing, supported by the presence of relevant clinical signs or symptoms (Caron et al., 2020). Depending on the disease progression and severity of these manifestations, patients with HD can be divided into different diagnostic categories, the ultimate one being manifest HD (or Stage 3) (Reilmann et al., 2014; Tabrizi et al., 2022). In the case of juvenile onset, symptoms are somewhat different, primarly manifested as hypokinesia with seizure often co-occuring (Nopoulos, 2016). Furthermore, if the patient's HD symptoms do not get genetically confirmed, a clinician should consider various alternative diagnoses (Martino et al., 2012). To further delve into the clinical profile of HD patients, the following section addresses clinical manifestations of HD in greater depth.

1.5 Clinical manifestations

Clinical **symptomatology** of HD is characterized by a variety of movement disturbances, a decline in cognitive functioning, and psychiatric abnormalities (Cardoso, 2014; Stoker et al., 2022). However, the specific combination and sequence of these manifestations may be significantly heterogeneous in different individuals (Cardoso, 2020; Roth, 2019). The course of the disease typically starts with minor cognitive and psychiatric disturbances, which are later accompanied by slight motor changes (Stoker et al., 2022). These motor abnormalities tend to become more pronounced and visible during the midstage of the disease, and together with the cognitive decline, reach their peak severity in the advanced stages, naturally resulting in a loss of autonomy (Kremer, 2002; Stoker et al., 2022). Additionally, it is important to note that despite motor disturbances being considered the most prominent (Ross et al., 2019), it is the cognitive and psychiatric symptoms that are often reported as more troubling for both patients and their caregivers (Anderson & Marshall, 2005). Due to the excess and diversity of clinical manifestations associated with HD, each group of symptoms (motor, cognitive and psychiatric) is discussed separately in the subsequent sections. For better clarification, we provide a list of these manifestations in the following Figure 3.

Figure 3. List of clinical manifestations associated with HD



*Hyperkinetic motor symptoms are also associated with cachectization (Stoker et al., 2022), which is not listed here as it does not specifically belong to any of the presented group of symptoms.

*Note: In general, there are three main groups of clinical manifestations associated with HD: motor, cognitive, and psychiatric (Stoker et al., 2022). The **motor** group encompasses a variety of hypekinetic and hypokinetic symptoms, along with less specific impairments (Kremer, 2002). The **cognitive** symptoms mainly include executive dysfunction, though other domains, apart from language, are often affected as well (Cardoso, 2014). The last group is defined by a plethora of **psychiatric** manifestations, including common symptoms, such as apathy and depression, as well as other behavioral alterations associated with HD (Craufurd & Snowden, 2002).*

1.5.1 Motor symptoms

Motor onset in HD typically starts with the presence of hyperkinetic disorders due to the disruption of the indirect corticostriatal pathway (Jiang et al., 2013; Nopoulos, 2016). The inability to inhibit involuntary movements is often attempted to be masked by using intentional voluntary movements, but these symptoms become increasingly evident as the disease advances (Paulsen & Conybeare, 2005). Later on, the hyperkinetic stage progresses into to a hypokinetic stage (Stoker et al., 2022), resulting from the disturbance of the direct corticostriatal pathway responsible for the initiation of voluntary movements (Jiang et al., 2013; Ruiz et al., 2000). In this stage, the person begins to have problems

initiating movements and therefore become slower, which, together with overall weakness, reflects signs of parkinsonism (Caron, 2020; Roth, 2019).

Movement abnormalities in HD manifest as either typical extrapyramidal signs and/or less specific movement impairments (Kremer, 2002). The hyperkinetic extrapyramidal symptoms[3] primarily include chorea, dystonia, akathisia, motor impersistance, as well as myoclonus, tic disorder, and tremor. In contrast, the hypokinetic extrapyramidal syndrome predominantly present as parkinsonism, particularly a combination of bradykinesia, rigidity, and postural instability, which can later result in akinesia (Kremer, 2002; Novak & Tabrizi, 2011; Reilmann, 2019; Stoker et al., 2022). Moreover, less specific motor impairments that can occur in patients with HD include oculomotor disturbances, gait disorder, dysarthria, dyspahgia, and nocturnal movements (Herzog-Krzywoszanska & Krzywoszanski, 2019; Kremer, 2002; Novak & Tabrizi, 2011; Stoker et al., 2022). For better understanding and clarification, we now provide deeper descriptions of all the motor symptoms mentioned above.

Starting with the hyperkinetic extrapyramidal symptoms, the most characteristic motor feature of HD is ***chorea***, which can be described as spontaneous, irregular, and excessive jerky movements (Kremer, 2002; NINDS, 2023). In the early stages of the disease, this may be seen as restlessness, for example, through fidgeting movements of fingers and hands while walking or even during the night (Kremer, 2002; Stoker et al., 2022). Slowly, facial muscles start to be affected, resulting in involuntary grimacing, cheek spasms, lip pouting, and eyebrow raising (Kremer, 2002). Simultaneously, chorea of neck muscles manifests as head turning and/or rotating, and the involvement of the appendicular musculature causes irregular body movements (Kremer, 2002; Rojas et al., 2022). As the disease progresses, chorea begins to affect proximal parts of the body (Rojas et al., 2022), which can be observed as repetitive flexing and extenting of the individual's toes and fingers, and/or frequent crossing and uncrossing legs (Kremer, 2002; Paulsen & Conybeare, 2005). Furthermore, choreic movements tend to worsen over time, often co-occurring with psychiatric disorders, such as depression and anxiety (Novak & Tabrizi, 2011). However, while chorea is the most common movement disorder in HD, it is not always present, which can alongside explain the inappropriateness of the name Huntington's chorea (Cardoso, 2014).

[3] Patients with HD often experience a gradual weight loss (cachectization), which is usually associated with the excessive movements mainly due to high caloric demands (Roth, 2019; Stoker, et al., 2022).

The next hyperkinetic symptom frequently present in patients with HD is ***dystonia,*** which can manifest as either dystonia secondary to HD or drug-induced dystonia (Ha & Jankovic, 2011; Novak & Tabrizi, 2011). Dystonia results from involuntary muscle contractions that lead to abnormal postures (e.g., of extremities) and repetitive movements, such as twisting of head and neck, and rotations of the shoulders (Kremer, 2002; Rojas et al., 2022; Roth, 2019). This manifestation can occur early in the disease, for instance, in the form of cervical dystonia (Rojas et al., 2022) and can be challenging to distinguish from symptoms of chorea, as these motor abnormalities tend to merge together (Kremer, 2002).

Another common phenomenon in HD patients is ***motor impersistence***, where the patient is often perceived as clumsy with tendency to lose grip (Shannon, 2011). This manifestation affects voluntary muscles, particularly causing the individual to be unable to sustain the contractions of their voluntary muscles in a consistent manner (Stoker et al., 2022). During motor assessments, this can be observed, for example, in the form of tongue protrusion, when patient is asked to keep the tongue out (McGarry & Biglan, 2017; Stoker et al., 2022).

The nature of repetitive movements can also be captured within the symptoms of ***akathisia*** (Gib & Lees, 1986). However, in this case, they are attributed to excessive subjective restlessness that makes the individual feel uncomfortable (Gib & Lees, 1986; Novak & Tabrizi, 2011). In addition, this appearance of discomfort can be easily misinterpreted as anxiety or overall agitation (Novak & Tabrizi, 2011).

Some of the less frequent hyperkinetic extrapyramidal abnormalities appearing in HD include ***myoclonus, tics (or tourettism)*** and ***tremor*** (Kremer, 2002; Roth, 2019). Myoclonus refers to jerky contractions of various muscle groups that are short and spontaneous (Novak & Tabrizi, 2011; Roth, 2019). There is a higher probability of myoclonus occurring in cases of juvenile HD, where it is often misdiagnosed as seizures (Carella et al., 1993; Novak & Tabrizi, 2011). Tics in HD can manifest as short and recurrent movements (e.g., blinking, nose flickering, or abnormal posturing), as well as vocal sounds (e.g., coughing, sniffing, wheezing, murmuring). Moreover, similar to previously mentioned motor symptoms, tics are also considered to have an involuntary basis (Novak & Tabrizi, 2011). Tremor is commonly defined as an involuntary and repetitive movement of an individual's somatic part (Elble, 2017). When present in HD, tremor usually occurs in the form of essential tremor, specifically postural and rest tremor (Rudzinska et al., 2013).

The predominant hypokinetic extrapyramidal syndrome in HD is ***parkinsonism***, typically associated with symptoms of ***bradykinesia***, ***rigidity***, and ***postural instability*** (Reilmann, 2019). Generally, bradykinesia can be observed as slowness of movements and is often mistaken for hypokinesia – sparse movements, opposite to hyperkinesia (Schilder et al., 2017). Accordingly, a rigid individual usually displays stiff and inflexible musculature (American Psychological Association [APA], n.d., "Rigidity"), which takes a form of difficulty to reposition (APA, n.d., "Muscular Rigidity"). Furthermore, postural instability in HD patients can be seen as deficiency in controling the one's posture, often resulting in falls (Reilmann, 2019). Finally, the aforementioned triad of parkinsonian symptoms may progress into akinesia[4], the inability to initiate movements (Reilmann, 2019; Schilder et al., 2017).

Continuing on the topic of less specific motor impairments, ***oculomotor disturbances*** belong to some of the earliest notable signs in HD, affecting the preponderant majority of the patients (Kremer, 2002). According to Lasker & Zee (1996), the most prominent eye movement disorder in HD involves alteration of saccadic movements. Examples of these include difficulties with maintaining a fixed gaze, where patient fails to supress spontaneous saccades when new visual stimuli appear. Another common issue is the struggle to initiate intentional saccadic movements, leading to delayed activation of these rapid eye motions. In clinical settings, this problem can be seen in patients who, toss their head or use blinking to initiate eye movements. Finally, oculomotor impairments tend to progress to significantly slower and reduced eye movements, primarily affecting vertical saccades but also resulting in deficiencies in smooth pursuit (Lasker & Lee, 1996).

Similarly to the oculomotor disturbances, ***gait disorders*** may manifest early in the disease in the form of sligh gait changes (Kremer, 2002). Typically, it is difficult to fully capture as it results from four previously mentioned movement disorders: chorea, dystonia, rigidity and ataxia (Stoker et al., 2022). Therefore, signs of gait disturbances can be observed mainly in complications in tandem walking, difficulty stopping when commanded, as well as turning (Kremer, 2002). These patients often show balance problems, which they tend to mask or compensate for with abnormal postures (Grimbergen et al., 2008). As the disease progresses, gait disorder becomes more pronounced, leading to falls, often confine the patient to a wheelchair (Kremer, 2002). Additionally, HD patients

[4] The co-occurance of akinesia with rigidity results in the so-called "akinetic-rigid syndrome", which typically appears in the late stages of HD. In juvenile cases of HD, this syndrome tends to manifest together with dystonia (Praveen & Madhuri, 2007).

tend to walk slower to avoid falls and their possible subsequent injuries (Grimbergen et al., 2008).

The majority of the patients also manifest speech difficulties, or ***dysarthria*** (Kremer, 2002), due to disrupted coordination of speech muscles and/or their overall weakness (Bryant, 2014). Among the main speech abnormalities associated with HD are fluctuations in speech rhythm and pace, resulting in disturbed articulation, which may later lead to the inability to speak (Caron, 2020; Kremer, 2002; Roth, 2019).

Dysphagia also tends to occur in HD, and can be understood as a deficit of swallowing (Kremer, 2002). It usually appears in the late stages of the disease and presents as difficulty swallowing food or liquids (Kremer, 2002; Roth, 2019). Aspiration of food is a common phenomenon in patients with dysphagia, resulting in symptoms such as coughing, vomiting after food, and recurrent infections related to the respiratory system called respiratory pneumonia (Dent & Shannon, 2022; Roth, 2019). Furthermore, food aspiration may lead to eventual choking, which often results in death (Kremer, 2002).

Last but not least, ***nocturnal movements*** are a significant source of disturbance for patients with HD (Anderson & Marder, 2001). In the initial stages of the disease, excessive choreic movements and dyskinesias can lead to difficulties falling asleep, frequent nighttime awakening, and subsequent struggles to fall back asleep (Anderson & Marder, 2001; Herzog-Krzywoszanska & Krzywoszanski, 2019; Rosenblatt, 2007). Conversly, as reported by Herzog-Krzywoszanska & Krzywoszanski (2019), bradykinetic features and rigidity present common challenges in the later stages, as they cause difficulties in changing positions in bed. Typically, there are two most frequently recorded abnormalities associated with excessive movement activity during sleep: 1) Periodic limb movements, manifested as rapid motions of a repetitive and stereotyped nature occuring during sleep; and 2) Resless leg syndrome, characterized by uncontrollable urges to move one's legs, which may result from an attempt to alleviate the symptoms (Herzog-Krzywoszanska & Krzywoszanski; 2019). Noctural movements, along with other sleep disturbances, naturally result in poorer sleep quality and subsequently decreased quality of life (Goh et al., 2018). Hence, non-motor sleep alterations will be discussed in section 1.5.3 Psychiatric symptoms.

1.5.2 Cognitive symptoms

Cognitive onset in HD is characterized by subtle changes in cognition that may occur years before the course of motor symptoms begin (Paulsen et al., 2017). These minor disturbances, for instance in psychomotor speed, typically present with a gradual onset and insidious progression. On the other hand, deficits in domains such as memory tend to have a more acute onset, occuring closer to the clinical course of the disease, with incremental progression (Montoya et al., 2006b).

Early in the disease, cognitive deterioration tends to be more domain-specific, with executive functions being predominantly affected (Montoya et al., 2006b). However, as the disease advances, a global disruption of cognitive functioning emerges, known as neurocognitive disorder (Roth, 2019). The neurocognitive disorder is one of the key features of HD, associated with slower information processing and intereference with everyday activities (Craufurd & Snowden, 2002; Montoya et al., 2006b). Importantly, cognitive deterioration in HD results from disruption in the corticostriatal circuit (Craufurd & Snowden, 2002), which is therefore referred to as subcortical dementia (Cardoso, 2014). Additionally, it is necessary to mention that the severity of cognitive symptoms is highly variable among different individuals.

As indicated before, the main **cognitive symptom** in HD concerns deficit in executive functions, such as decision-making, inhibitory control, planning and judgement, working memory, problem-solving, mental flexibility, and organizing (Cardoso, 2014; Craufurd & Snowden, 2002). Other affected domains include attention, learning and memory, visuospatial abilities, and social cognition (Dumas et al., 2012; Stoker et al., 2022). Patients with HD also display an overall slowing of processing speed, known as bradyphrenia (Cardoso, 2014; Craufurd & Snowden, 2002), as well as a lack or complete loss of insight (anosognosia), which creates difficulties for patients in reporting information regarding their cognitive functioning (Dumas et al., 2012; Paulsen et al., 2017).

One of the earliest affected cognitive domains in HD is that of the ***executive functions (EF)*** (Craufurd & Snowden, 2002). EF can be described as a set of cognitive abilities necessary for controlling and regulating other cognitive processes with the overall aim of goal-oriented behavior (Craufurd & Snowden, 2002; Harvey, 2019; Paulsen et al., 2017). Some of the initial signs of impaired EF may include difficulties with decision-making and disrupted inhibitory control, often reported as frequent “jumping to

conclusions" (Heim et al., 2020). Additionally, patients with HD tend to exhibit planning deficits associated with poor judgment and a lack of foresight (Craufurd & Snowden, 2002). Moreover, an important feature of planning abilities is working memory, which is commonly affected in patients with HD (Lawrence et al., 1996; Migliore et al., 2021). Simultaneously, poor planning also relates to the insufficient problem-solving skills, manifesting as an inability to effectively use feedback and develop meaningful strategies (Craufurd & Snowden, 2002). Furthermore, relatives of HD patients typically describe their thinking as rigid and inflexible, which naturally signals limited mental flexibility (Craufurd & Snowden, 2002; Migliore et al., 2021). Finally, the actions of these individuals are often disorganized, which contributes initially to professional/occupational ineffectiveness and, later, to an inability to perform regular daily activities (Craufurd & Snowden, 2002; Roth, 2019). In turn, one of the initial and most prevalent cognitive impairments reported in individuals with HD is the slowing of ***processing speed (or bradyphrenia)*** (Paulsen et al., 2017). Consequently, slower information processing appears to negatively affect performance on cognitive tests, particulary on time-dependent tasks (Craufurd & Snowden, 2002). Nonetheless, according to Paulsen et al. (2011) this overall slowing arises as a result of so-called effortful processing, where the brain attempts to compensate for the impairment by engaging other regions to perform the task. In parctice, this may be noticeable in patients who need more time to complete assignment, although their accuracy may remain intact (Paulsen, 2011). In addition, patients often find these tasks exhausting, as they require greater mental effort and more attention, the latter of which, as previously mentioned, also declines in HD (Paulsen, 2011; Paulsen et al., 2017).

Another problematic cognitive aspect of patients with HD is ***attention*** (Stoker et al., 2022). According to Harvey (2019), attention generally consists of two main components: 1) the ability to maintain focus over an extended period (sustained attention, or vigilance); and 2) the ability to focus on relevant information while ignoring irrelevant distractors (selective attention, including divided attention). Additionally, it is important to note that these skills also involve components of executive functioning (Harvey, 2019). Therefore, attentional deficiencies can naturally lead to disruptions of higher-order cognitive functions (Paulsen et al., 2017). One of the most common attentional deficits in HD is reported to be difficulty shifting attention (Stoker et al., 2017). This issue may contribute to disrupted inhibitory control in working memory tasks, as patients tend to perseverate on their responses instead of shifting attention to the novel stimuli (Paulsen & Conybeare, 2005; Paulsen et al., 2017). Moreover, individuals with HD often exhibit difficulties in allocating

their mental resources to different stimuli. Generally, a decline in attention can lead to challenges in handling multiple tasks simultaneously (Craufurd & Snowden, 2002). In the advances stages of the disease, this may result in an inability to perform some tasks like talking while walking, for instance, a patient might stop walking in order to answer a question (Craufurd & Snowden, 2002).

Some of the important and frequently studied cognitive manifestations associated with HD are ***learning*** and ***memory*** (Butters et al., 1985; Montoya et al., 2006a). Taxonomically, long-term memory can be divided into declarative (or explicit) memory and non-declarative (or implicit) memory (Werning & Cheng, 2017). Implicit memory is sometimes referred to as motor memory because it stores information related to our motor abilites, such as driving a car, or playing an instrument (Paulsen, 2011; Werning & Cheng, 2017). On the other hand, explicit memory involves information about our personal experiences (episodic memory) as well as the factual knowledge (semantic memory) (Montoya et al., 2006a; Werning & Cheng, 2017). The most affected memory system in HD is episodic memory, typically assessed by tasks that require recall and recognition of the information (Cavallo et al., 2022; Montoya et al., 2006a). As noted in Montoya et al. (2006a), in the past, research typically showed significant deficits in recall with spared recognition skills in patients with HD. However, it is now known that recognition may be also significantly impaired in these patients. Nonetheless, a notable difference, where recognition is more or less spared, is still often reported in individuals with mild cognitive impairment (Montoya et al., 2006a). Therefore, abnormalities in episodic memory in HD are associated with both: 1) deficits in encoding information from working memory to long-term memory, leading to impairments in recognition; and 2) alterations in retrieving previously learned information from memory storage, commonly manifested as failures in delayed recall tasks (Harvey, 2019; Montoya et al., 2006a; Paulsen, 2011; Paulsen & Conybeare, 2005).

Another domain affected with gradual progression is the one of ***visuospatial abilities*** (Montoya et al., 2006b). Visuospatial functioning is characterized by visual perception and the identification of different objects, along with processing information regarding their spatial relationships (Pal et al., 2016). This can be assessed using visuoconstructional tasks, such as copying geometric figures, and solving puzzles (Craufurd & Snowden, 2002; Paulsen & Conybeare, 2005). In HD, difficulties with performing such tasks arise from deficiencies in spatial manipulation of the given material (Labuschagne et al., 2016). Moreover, memory for visuospatial information is impaired as

well, typically with allocentric spatial memory declining early in the disease, while egocentric spatial memory deteriorates with disease progression (Paulsen & Conybeare, 2005). Impairment in allocentric spatial memory leads to an inability to process spatial relationships among different objects, such as reading the maps and maintaining an overall sense of directions (Paulsen & Conybeare, 2005; Pirogovsky et al., 2015). On the other hand, disruptions in egocentric spatial memory cause misjudgement of information regarding objects and their distances, such as walls, curbstones, and other possible obstructions, in relation to the one's body (Paulsen & Conybeare, 2005).

Subsequently, deficits in ***social cognition*** have also been reported as an early feature of HD, with gradual worsening over time (Turner et al., 2022). Generally, social cognition encompasses four core factors: 1) emotional recognition (or social perception), which refers to the ability to recognize emotional cues from others, such as facial or vocal expressions; 2) awareness and reactivity (or social behavior), involving the understanding of one's own emotions and the ability to properly communicate them in various social interactions; 3) Theory of Mind, or the ability to comprehend the mental states of others while respecting their possible diversity from one's own perspective; and 4) empathy (or affective empathy), which represents the capacity to perceive emotional states of others and provide appropriate emotional feedback in a given situation (Mason et al., 2021; Turner et al., 2022). Of the aforementioned domains of social cognition, emotional recognition is the most extensively examined. The corresponding studies typically report alterations in the recognition of primarily negative emotions, particularly disgust, but also fear, anger, and sadness (e.g. Dumas et al., 2002; Henley et al., 2012; Paulsen, 2011). Although most studies focus on the deficits in emotional recognition, Turner et al. (2022) suggest that other social cognition domains are affected as well, with Theory of Mind and emotional recognition showing the most significant impairments. Furthermore, as the disease progresses, the decline in social cognition often leads to difficulties in handling social interactions, which contributes to the individual's functional decline and increases the burden on caregivers (Paulsen et al., 2017; Ramos & Garrett, 2017).

Ultimately, we will shift our attention to the ***language*** domain. When discussing linguistic impairments, it is necessary to differentiate between the: 1) cognitive alterations in the ability to speak and comprehend spoken language (aphasias); and 2) motor abnormalities leading to altered speech production (dysarthria) (Craufurd & Snowden, 2002). Although patients with HD often suffer from dysarthria, their linguistic abilities tend to remain relatively intact thorughout the entire course of the disease (Cardoso, 2014;

Craufurd & Snowden, 2002). Despite this, Craufurd & Snowden (2002) noted that these patients tend to show poorer performance on language tasks, which can be attributed to dysfunction in particular executive components. For instance, mental inflexibility may lead to deficits in phonemic fluency, while impaired retrieval may cause altered categoric fluency. Moreover, difficulties with performing language tasks in the later stages of the disease are often related to high attentional demands (Craufurd & Snowden, 2002). To conclude, it is important to keep in mind that even patients with advanced HD, whose speaking ability deteriorates, are likely to comprehend spoken language (Paulsen, 2011).

Another important deficit associated not only with cognitive, but also with motor and psychiatric symptoms, is the ***lack of insight (or anosognosia)*** (Paulsen et al., 2017). Due to their unawareness, patients with HD often overestimate their actual abilities across all three domains, while underestimating the severity of their impairments. Moreover, the lack of insight is often misunderstood by those around the patient as deliberate or willful ignorance of the symptoms. Therefore, it is important to communicate this issue to the patient's caregiver and/or family to avoid additional and avoidable difficulties in day-to-day living (Paulsen et al., 2017).

1.5.3 Psychiatric symptoms

Psychiatric onset in HD is significantly less predictable than the onset of motor and cognitive symptoms, as it can occur at any stage of the disease (Anderson & Marder, 2001). However, subtle behavioral changes often begin as initial manifestations, years before a motor diagnosis (Roth, 2019). These initial phases of the disease are usually characterized by increased irritability, impulsive behavior, and mood disturbances, which are commonly interpreted by family members as personality changes. As the disease advances, apathy frequently arises and is usually misunderstood by relatives as depression (Nopoulos, 2016). Notably, psychiatric disturbances in HD are often the primary reason for seeking help, as they significantly contribute to the overall strain of the disease on both patients and their caregivers (Ramos & Garrett, 2017; Paulsen et al., 2017).

As previously mentioned, one of the most common **psychiatric symptoms** in HD is depression, often accompanied by suicidal ideations (Nopoulos, 2016). Other widespread psychiatric manifestations include apathy, anxiety, as well as various obsessions and compulsions (Stoker et al., 2022), accompanied by irritability and

aggression. On the other hand, psychotic symptoms, such as delusions and hallucinations may occur, but are quite rare (Craufurd & Snowden, 2002; Rosenblatt, 2007; Stoker et al., 2022). Additional symptoms associated with HD encompass various sexual dysfunctions as well as impulsivity, which is linked with risk-taking behaviors, such as mania and substance abuse (Craufurd & Snowden, 2002; Johnson et al., 2017; Morris et al., 2022). Sleep disturbances may also be present, however, they are not solely psychiatric manifestations, as they can partially overlap with, or becaused by, motor symptoms (Craufurd & Snowden, 2002). Nonetheless, these symptoms vary greatly in severity and differ from one individual to another, often worsening over time and significantly impacting daily functioning and patient's quality of life (Paulsen et al., 2017). Thus, for better comprehension and coherence, we will now examine each of the aforementioned psychiatric symptoms separately.

Apathy can be described as a loss of interest and motivation that usually occurs in middle to later stages of the disease. In day-to-day living, it can manifest as a lack of inititative, for instance, the patient may appear less proactive with diminished reactivity to events (Craufurd & Snowden, 2002). Disengagement, reduced activity, and quietness can mimic symptoms of depression, however, apathy presents without associated sadness, dysphoria and other depressive symptoms (Goh et al., 2018; Rosenblatt, 2007). Importantly, apathy is usually more distressing for family members and friends than for the patients themselves (Rosenblatt, 2007). Therefore, educating the individual's relatives can help increase awareness of typical difficulties linked to HD, as well as assist them in managing their own behaviors and attitude towards the patient (Anderson & Marder, 2001; Rosenblatt, 2007). Additionally, apathy tends to progressively worsen over time and quite rapidly, partially due to its unresponsiveness to drug treatment such as antidepressants (Ramos & Garrett, 2017).

Another typical psychiatric manifestation, which is simultaneously one of the most common early symptoms exihibited in HD, is ***depression*** (Anderson & Marshall, 2005; Nopoulos, 2016). The lifetime prevalence of depressive symptoms in HD is estimated to be 30-40% (Rosenblatt, 2007), with declining prevalence throughout the course of the disease (Nopoulos, 2016). Despite this, it is frequently difficult to diagnose depression in these patients as other symptoms, such as apathy or weight loss, may be misunderstood for it. Conversely, it can also be easily underdiagnosed by simply dismissing its symptoms, such as social withdrawal and hopelessness, as typical intelligible responses or signs of HD (Rosenblatt, 2007). Nonetheless, in some cases, the reactive nature of depression may

appear as a form of psychological feedback to the illness. However, in most cases, these symptoms typically precede motor onset, making it unlikely that the patient is depressed due to a positive HD diagnosis they have not received yet (Craufurd & Snowden, 2002). Furthermore, even mild forms of depression can aggrevate cognitive and functional impairment, consequently leading to a lower quality of life for the patient (Craufurd & Snowden, 2002; Paulsen et al., 2019). Notably, depression is one of the very few treatable symptoms of HD, therefore, early detection followed by effective intervention is a crucial aspect of improving their quality of life (Ramos & Garrett, 2017).

Together with depression, ***suicidial ideations*** have been consistently reported since the initial descriptions by George Huntington (Craufurd & Snowden, 2002). Generally, two crucial periods of higher suicidality risk have been noted: 1) suicidal thoughts are often a symptom of depression, which typically occurs years before the diagnosis is established; and 2) the risk of suicide increases with the onset of the early symptoms that eventually lead to noticeable functional decline (Goh et al., 2018; Nopoulos, 2016). The first case, naturally emphasizes the importance of early detection and subsequent treatment of depressive symptoms as a preventative measure (Paulsen et al., 2017). In the second situation, mainly therapeutic intervention may be particularly useful, as the idea of suicide often helps the patient to retain the sense of autonomy and control over their own life (Craufurd & Snowden, 2002). Moreover, suiciduality may also be associted with cognitive alterations, particularly difficulties with inhibitory control as part of executive dysfunction (Goh et al., 2018; Paulsen et al., 2017). Therefore, as the disease progresses, significant cognitive decline, along with symptoms like apathy or emotional numbness, decreases the risk of suicide (Craufurd & Snowden, 2002). Interestingly, suicide is markedly more common in HD than in other neurological disorders. Therefore, it is important that clinicans are aware of these critical periods as well as the high prevalence of suicidality among HD patients. (Paulsen et al., 2017).

A further common psychiatric symptom in HD is ***anxiety***, which, similarly to the two abovementioned manifestations, can occur in the initial stages of the disease (Anderson & Marder, 2001). According to Dale & Duijn (2015), research indicates that anxiety does not align with the progression of the disease, and there are no marked differences in clinical signs between premanifest gene carriers and those with manifest HD. This suggests that the development of anxiety in these patients is more likely independent rather than a direct consequence of HD pathology (Dale & Duijn, 2015). However, it is possible that some patients experience excessive worry as a response to the progressive

and irreversible nature of the illness, often accompanied by irritability (Anderson & Marder, 2001; Dale & Duijn, 2015). In everyday life, patients may engage in additional indicative acitivities such as pacing, or tapping, which, combined with increased agitation, can lead to interpersonal challenges (Dale & Duijn, 2015; Goh et al., 2018). Additionally, anxiety is commonly highly comorbid with depression as well as suicidal ideations. Therefore, identifying and subsequently treating anxiety symptoms is crucial, as it can significantly improve the patient's quality of life and functional capacity (Dale & Duijn, 2015). Intriguingly, both males and females with HD are equally affected by anxiety, which contrasts with its prevalence in the general population (Paulsen, et al., 2017).

To expand on the topic of common behavioral manifestations, rates of ***obsessions*** and ***compulsions*** are found to be higher in patients with HD than in the general population (Anderson et al., 2010). This is thought to be due to the similar underlying pathophysiology of HD and obsessive-compulsive disorder, specifically the disruption of corticostriatal circuitry (Anderson et al., 2010; Zadegan et al., 2023). Consequently, intrusive thoughts and repetitive behaviors tend to become more prevalent as the disease progresses, with gradual worsening over time (Paulsen et al., 2017). Some of the most common obsessive-compulsive behaviors in HD include repetitive checking, excessive cleaning, engagement in repetitive rituals, and fixation on peculiar idiosyncratic subjects (Ramos & Garrett, 2017; Rosenblatt, 2007). Maladaptive impulses, such as pathological gambling, as well as affective obsessions and/or compulsions with aggressive aspects, have also been observed (Anderson et al., 2010; Ramos & Garrett, 2017). Additionally, Andeson et al. (2010) reported frequent co-occurance with other clinical manifestations, including: 1) motor symptoms, where the severity of obsessive-compulsive symptoms was correlated with more bradykinetic and fewer dystonic features; 2) cognitive symptoms, particularly executive dysfunction, such as the inability to swich attention when required; and 3) comorbidity with other psychiatric symptoms, including depression, suicidality, aggression, and psychotic symptoms (Anderson et al., 2010). Notwithstanding, symptoms of obssesions and compulsions are sometimes mistaken for perseverative behaviors, which also occur in HD (Paulsen et al., 2017). However, it is important to note that these behaviours result from cognitive and emotional inflexibility, with a fundamentally different neuropathology compared to HD and obsessive-compulsive symptoms (Paulsen et al., 2017; Zadegan et al., 2023).

The most troubling yet widespread behavioral abnormalities in HD are ***irritability*** and ***aggresion***, which can lead to harm for both oneself and others (Anderson & Marshall,

2005; Craufurd & Snowden, 2002). These symptoms usually begin in the premanifest stage, independent from gender, and gradually worsen as the disease progresses (Craufurd & Snowden, 2002; Karagas et al., 2020; Paulsen et al., 2017). As stated in Craufurd & Snowden (2002), affected individuals are typically easy to provoke, leading to outbursts of anger and violence. This detrimental behavior is often directed at a specific member of family, usually the caregiver, which can significantly impact their relationship. As a result, carers frequently hesitate to express their concerns in front of the patient and therefore, should be interviewed separately during clinical visits. Moreover, these behaviors often co-occur with other psychiatric manifestations, most alarmingly suicidal ideations, which are frequently reported by patients after angry outbursts. Therefore, educating the patient's family can enhance their understanding of the nature of symptomatology and serves as a preventative measure in critical situations (Craufurd & Snowden, 2002). Additionally, irritable mood and aggressive behavior may sometimes be mistaken for agitation, restlessness, or even antisocial personality disorder, highlighting the importance of a thorough assessment (Anderson & Marder, 2001; Ramos & Garrett, 2017).

Although less frequent, ***psychotic symptoms***, including ***delusions*** and ***hallucinations*** are nonetheless significant (Rosenblatt, 2007). They usually occur either before the motor diagnosis or in patients with early disease onset, and their prevalence typically decreases over time (Anderson & Marshall, 2005; Craufurd & Snowden, 2002; Goh et al., 2018). Symptoms of psychosis are often accompanied by emotional numbness, social withdrawal, and a diminshed sense of violation, which naturally creates an additional stressor for both patients and their caregivers (Craufurd & Snowden, 2002). The most consistently reported delusions involve beliefs of prosecution, though erotomanic, parasitic, and hypochondrical delusions may also be present (Anderson & Marshall, 2005; Goh et al., 2018; Rosenblatt, 2007). Similar to schizophrenic symptoms, the most common hallucinations are auditory in nature (Rosenblatt, 2007). Additionally, a challenging aspect of these symptoms is their treatment, as commonly used typical antipsychotics often contribute to extrapyramidal manifestations and exacerbate cognitive deterioration (Craufurd & Snowden, 2002; Rosenblatt, 2007).

A problematic but highly understimated aspect of HD is ***sexual dysfunctions***, which has been widely documented since the early descriptions of the disease (Rosenblatt & Leroi, 2000; Szymus et al., 2020). Although early studies primarily focused on hypersexuality, newer research has shown that hyposexuality is actually more prevalent in these patient (Kolenc et al., 2015). More specifically, hyposexual abnormalities most

commonly involve loss of libido (or reduced sexual desire) and orgasmic inhibition (Craufurd & Snowden, 2002; Rosenblatt et al., 2000; Schimdt & Bonelli, 2007). Other sexual dysfunctions may include various paraphilias, such as exhibitionism, voyeurism, pedophilia, as well as other inappropriate sexual behaviors, such as promiscuity, an sexual aggression (Anderson & Marshall, 2002; Craufurd & Snowden, 2005; Rosenblatt et al., 2000). In relation to the psychiatric manifestations found in HD, alterations in sexual functioning may co-occur with mania, depression, irritability, apathy, and hallucinations (Szymus et al., 2020; Rosenblatt et al., 2000). Moreover, sexual disorders may appear in the early stages of the disease and worsen along with the disease progression, causing a significant decrease in the quality of patient's life (Kolenc et al., 2015; Kolenc et al., 2017; Szymus et al., 2020).

Subsequently, ***impulsive behaviors*** have consistently been reported among a number of patients. Similar to most other psychiatric symptoms, they occur early in the disease and worsen over time (Morris et al., 2022). Impulsivity can be described as a combination of fast, spontaneous actions and a lack of unawareness of their consequences. This type of behavior is commonly associated with risk-taking activities seen in other behavioral manifestations of HD, such as mania, and substance abuse. Additionally, it seems necessary to mention that impulsivity is closely linked to cognitive alterations, in particular executive dysfunction and attentional deficits (Johnson et al., 2017).

Mania and hypomania are less prevalent symptoms of HD, however, they occur more frequently than in the general population (Craufurd & Snowden, 2002). Manic or hypomanic episodes in HD are usually characterized by grandiosity, hyperactivity, and recklessness (Goh et al., 2018; Rosenblatt & Leroi, 2000). Nevertheless, they are also typically accompanied by other psychiatric abnormalities in HD, such as reduced sleep necessity, increased irritability, sexual misconduct, impulsivity, depression, and, in advanced stages, delusions and hallucinations (Craufurd & Snowden, 2002; Rosenblatt, 2007; Rosenblatt & Leroi, 2000).

In a similar manner, ***substance abuse*** is believed to be more prevalent in patients with HD than in wider society (Salinas Barboza et al., 2017). Previous studies commonly reported an earlier age of motor onset in patients, particularly women, with a history of abuse of various substances, such as tobacco, alcohol, and other drugs (Byars et al., 2012; Schultz et al., 2017). Contextually, substance abuse in HD is associated with elevated severity of motor, cognitive, and psychiatric symptoms, as well as exacerbation of these manifestations (Craufurd & Snowden, 2002; Ehret et al., 2007). Furthermore, these

patients are more prone to other behavioral changes, such as irritability, aggression, anxiety, depression, suicidal ideations, and sleep difficulties (Anderson & Marshall, 2005; Craufurd & Snowden, 2002; Salinas Barboza et al., 2017; Wetzel et al., 2011).

Sleep disturbances can occur from the early stages of the disease and present in the vast majority of HD patients (Goh et al., 2018; Herzog-Krzywoszanska & Krzywoszanski, 2019). The most common sleep alterations include insomnia, complication with both falling asleep and remaining asleep, REM sleep disorders, and frequent nocturnal interruptions, which may be accompanied by anxiety and choreic movements (Herzog-Krzywoszanska & Krzywoszanski, 2019; Rosenblatt, 2007). Additionally, these patients often experience chronic daytime fatigue, characterized by excessive sleepiness and difficulties staying awake, which can lead to uncontrolable falling asleep in inappropriate situations (Herzog-Krzywoszanska & Krzywoszanski, 2019). Common psychiatric comorbidities include depression, anxiety, mania, and apathy (Goh et al., 2018; Herzog-Krzywoszanska & Krzywoszanski, 2019). Furthermore, disruptions in the sleep-wake cycle may also be associated with cognitive deficitis, particularly impairments in inhibitory control, attention, processing speed, and executive functioning (Goh et al., 2018; Herzog-Krzywoszanska & Krzywoszanski, 2019; Ramos & Garrett, 2017). Naturally, changes in circadian rhythm and reduced sleep quality typically interfere with an individual's everyday activities, leading to increased distress and decreased life satisfaction (Goh et al., 2018; Herzog-Krzywoszanska & Krzywoszanski, 2019).

1.5.4 Phenotypic variants

Variability in the clinical presentation of patients with HD has been observed since the initial attempts to study these cases (Farrer & Conneally, 1987). One example of this phenotypic heterogeneity was illustrated in the study by Folstein et al. (1984), who presented two families with distinct symptomatic patterns of HD. In one family, members predominantly displayed psychiatric manifestations that preceded motor onset by several years, whereas in the other family, motor symptoms were predominant, with only subtle psychiatric changes (Folstein et al., 1984). Nowadays, we distinguish between three major HD phenotypes: motor, cognitive, and psychiatric, each characterized by a distinct clinical symptomatology (Hellem et al., 2021).

To begin with, it is well-established that the length of the CAG repeat is inversly correlated with the age of onset, disease severity, as well as its progression (Martinez-Horta et al., 2023). However, genetic predisposition accounts for only around 60% of this variability, leaving the remaining approximately 40% for the effects of environmental factors (Jiang et al., 2013; Martinez-Horta et al., 2023). These differences are particularly evident in patients with the same number of CAG triplets but markedly different rates of disease progression (Martinez-Horta et al., 2023). Therefore, studying the characteristic features of distinct HD phenotypes is crucial not only for understanding the heterogeneity of the disease but also for optimizing the treatment of these patients (Kremer, 2002).

The first to be discussed is the **motor phenotype**, which reflects the underlying neuropathology of the direct and indirect corticostriatal pathways (Jiang et al., 2013). In general, there are three variants of the motor phenotype: 1) the predominantly choreic variant, 2) the predominantly bradykinetic-rigid (or Westphal) variant, and 3) the mixed-motor variant (Hart et al., 2013).

Firstly, the ***"predominantly choreic variant"*** is characterized primarily by hyperkinetic choreic symptoms that are present in the early stages of the disease, and which later result to a more hypokinetic form (Jacobs et al., 2016). This variant can be also referred to as the typical HD phenotype and is associated with the average adult age of onset and a correlated length of the CAG repeats (see Figure 1) (Jacobs et al., 2016; Kremer, 2002). Additionally, this classical variant is marked by gradual disease progression (Kremer, 2002) and relatively spared cognitive functioning compared to the Westphal variant (Hart et al., 2013).

Secondly, the ***"predominantly bradykinetic-rigid (or Westphal) variant"*** is more common in younger patients, typically with juvenile or early adult onset, and is associated with a higher number of CAG triplets (Kremer, 2002). This variant is also linked to a more insidious progression of the disease (Stoker et al., 2022), and severe cognitive and psychiatric impaiments that are often present by early adulthood (Julayanont et al., 2020a). As the name already implies, this HD phenotype is characterized predominantly by hypokinetic motor impairments, such as bradykinesia and rigidity (Julayanont et al., 2020a; Kremer, 2002).

Thirdly, the ***"mixed-motor variant"*** encompasses both hyperkinetic and hypokinetic symptoms coexisiting in HD (Hart et al., 2013). Regarding non-motor manifestations, these patients exhibit more psychiatric disturbances, such as depression or apathy, compared to those with the predominantly choreic phenotype (Julayanont et al.,

2020a). However, they generally perform better on cognitive tasks than individuals with the Westphal variant.

A possible **cognitive phenotype** has been reported (Martinez-Horta et al., 2024). However, there is often significant variability in cognitive decline and the rate of its progression among patients with HD, even in those with the same CAG repeat length (Martinez-Horta et al., 2023).

Papoutsi et al. (2014) suggest that there might be additional mechanisms contributing to the deterioration of cognitive processes and global functioning. Specifically, neural compensation, or the ability to compensate for neuronal damage, plays an important role in determining the severity of symptoms and the overall progression of the disease. Simultaneously, this compensatory mechanism heavily relies on the individual's cognitive reserve, or the capacity to resist and cope with the underlying neurodegeneration, which increases with factors, such as general intelligence and years of education. Thus, highly educated patients are considered more resilient to neuronal damage, which can be observed in a later onset of symptoms or less cognitive impairment for the same degree of neurodegeneration compared to patients with lower education (Papoutsi et al., 2014).

In addition, Papoutsi et al. (2014) present two hypotheses related to these underlying neural mechanisms. Firstly, there is a possibility that greater cognitive reserve is associated with higher encoding efficiency, which leads to an increased capacity to handle cognitively demanding tasks. Secondly, it is hypothesized that highly educated patients possess a greater ability to incorporate new brain regions into already existing neural networks. This, in turn, results in better performance on tasks involving specific brain areas that are thought to be affected in patients with HD (Papoutsi et al., 2014).

Furthermore, Martinez-Horta et al. (2023) used the rate of disease progression in an attempt to distinguish between two cognitive phenotypes. Particularly, the phenotype with a ***"slow cognitive progression"*** profile is characterized by a gradual deterioration in cognitive and global functioning. On the other hand, patients with a ***"fast cognitive progression"*** pattern display a more aggressive rate of progression, associated not only with significantly worse cognitive and functional impairment but also with a longer duration and greater severity of motor symptoms (Martinez-Horta et al., 2023).

In relation to motor-manifest HD, Julayanont et al. (2020b) proposed three phenotypes of mild cognitive impairment (MCI) based on the predominance of the affected cognitive domain: 1) patients with ***"executive MCI"*** present impairments solely in

executive functions, including speed of processing; 2) ***"representational MCI"*** affects exclusively the memory and language domains; and 3) the occurance of ***"mixed executive-representational MCI"***, which exhibits as a combination of executive dysfunction and representational impairment. The most common of these phenotypes appears to be the mixed variant, which is simultaneously correlated with greater severity of motor manifestations and higher global dysfunction. Among the more specific variants, executive MCI was more prevalent than the reprenstational MCI. Therefore, the greatest cognitive impairment in these patients seems to be the disruption of executive functioning along with slow mental processing (Julayanont et al., 2020b).

A more recent study by Martinez-Horta et al. (2024) supports the evidence of cognitive variability among patients with HD. Unlike the previously mentioned studies, the authors emphasize the possible contributions of tauopathy[5] to this heterogeneity. Additionally, they noted that while executive dysfunction and slow processing speed are the most prominent cognitive features in HD, the deterioration of visuospatial and language abilities is associated with a more severe cognitive phenotype, which in turn is linked to a greater degree of tauopathy. Therefore, they suggest that more significant cognitive decline in HD patients could be explained by elevated amounts of tau protein, as measured by cerebrospinal fluid analysis (Martinez-Horta et al., 2024).

Lastly, an early attempt to categorize different variants of **psychiatric phenotypes** was made by Weigell-Weber et al. (1996), who, based on the predominance of specific symptoms, divided HD patients into four groups: 1) the individuals with ***"predominantly personality changes"***, including irritability and aggression; 2) the patients with ***"predominantly psychotic variant"***, such as delusions and hallucinations 3) those with ***"predominantly depressive variant"*** associated with mood dysregulation; and 4) the ***"non-specific alterations"*** in patients either without the psychiatric manifestations or without a single predominating group of symptoms.

However, the psychiatric phenotype is somewhat more complex and heterogeneous than the previously mentioned motor and cognitive variants (Tost et al., 2004). Therefore, studying psychiatric symptoms is particularly challenging for a variety of reasons (McAllister et al., 2021; Tost et al., 2004). For instance, initial behavioral changes often occur early in the disease and precede the motor onset by years (Tost et al., 2004). As a

[5] It has been proposed that, in addition to the already established disease modifiers (such as the number of CAG repeats), the levels of tau protein could contribute to the cognitive diversity among HD patients (Martinez-Horta et al., 2024).

result, the presence of these symptoms is usually recorded retrospectively, after the diagnosis of HD has been established (McAllister et al., 2021).

As De Souza (2015) pointed out, it is often difficult to confidently specify the etiology of these manifestations, as their nature cannon always be solely attributed to HD. Specifically, psychiatric symptoms may arise as a consequence of disease burden in gene carriers. These individuals are often exposed to significant stress from an early age, as they may witness the disease progression in affected family members. Another environmental factor contributing to the higher prevalence of psychiatric abnormalities, is the point of diagnosis itself. However, the common presence of these symptoms before the actual diagnosis and their relatively late age of their onset compared to the general population suggest additional contributing factors (De Souza, 2015).

One possible explanation focuses on the polygenic risk of psychiatric disorders, which may significantly contribute to the development of these associated symptoms (Ellis et al., 2019). Behavioral manifestations such as depression, irritability, aggression, and schizophrenia share similar genetic predisposition, leading to their frequent clustering and aggregation within HD families (De Souza, 2015; Ellis et al., 2019). Moreover, variations in coping mechanism (De Souza, 2015), which are associated with the previously mentioned concept of cognitive reserve (Papoutsi et al., 2014), may result in differences among these families (De Souza, 2015). For instance, individuals with greater intelligence are at significantly lower risk for developing schizophrenia and, consequently, for other associated conditions as well (Ellis et al., 2019).

Furthermore, differences in the severity of psychiatric manifestations have been also reported. The most pronounced abnormalities are found in cases of juvenile HD, suggesting at least a partial correlation with CAG repeat length (Weigell-Weber et al., 1996). However, while the lenght of this trinucleotid expansion is known to be linked with overall disease progression, only symptoms such as apathy and perseverative thoughts follow this trend. This suggests that the prevalence of most psychiatric symptoms is unrelated to the length of the CAG repeat (De Souza, 2015).

1.6 Neuroimaging evidence in Huntington disease

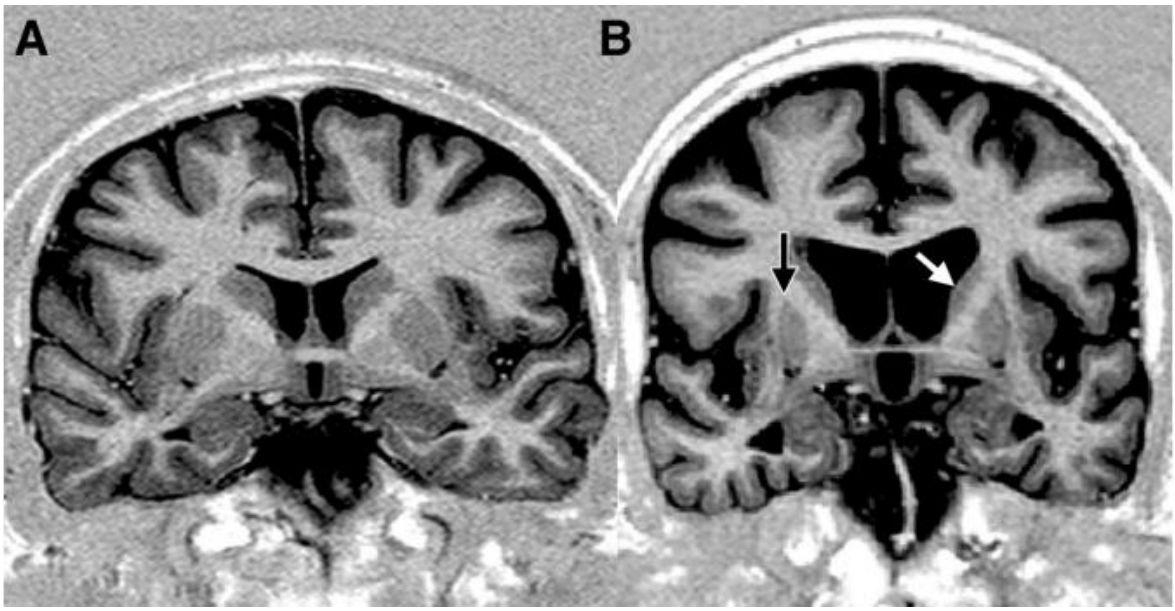
Over the past few decades, the use of various **neuroimaging techniques** has played a crucial role in advancing our understanding of the neuropathological processes in HD.

Particular emphasis has been placed on describing and comparing HD patients at different stages of the disease with asymptomatic individuals representing at-risk gene carriers (Niccolini & Politis, 2014). Thus, the main aim of this subchapter is to depict the key findings related to the underlying pathogenesis of HD, as revealed by in-vivo structural neuroimaging studies (Jiang et al., 2023).

Considering the range of structural neuroimaging studies performed, we specifically focus on those utilizing structural ***magnetic resonance imaging (MRI)***. In general, MRI is employed to measure morphological features of the brain and related changes resulting from disease pathology (Montoya et al., 2006b). These changes can be assessed by examining cortical thickness and/or the volume of different brain tissues, such as gray matter, white matter, or cerebrospinal fluid (Johnson & Gregory, 2019). In HD, this type of imaging is used to reveal the presence and extent of neural loss (or atrophy) in various brain regions and to track disease progression (Bogaard et al., 2011).

As previously mentioned, the main neuropathological feature of HD is atrophy in the frontal and subcortical areas, with a particular focus on the basal ganglia (Jiang et al., 2023). Specifically, the initial and most commonly reported anatomical change in these patients is the gradual neurodegeneration of the dorsal striatum, which includes the caudate nucleus, putamen, and nucleus accumbens (Bogaard et al., 2011; Goh et al., 2018), a core component of the ventral striatum (Salgado & Kaplitt, 2015). In addition, frequently decayed brain region is also globus pallidus (Goh et al., 2018), which, along with putamen, forms the lentiform nucleus (Hewitt, 1961). Moreover, decreasing gray matter volume has been observed in other structures, such as the thalamus, brainstem, hippocampus, amygdala, cingulate cortex, and insula (Bogaard et al., 2011; Morris et al., 2022). Over time, a reduction in overall brain volume and enlargement of the ventricles, with increased cerebrospinal volume, become evident (Brooks & Andrews, 2002; Hobbs et al., 2010). This suggests that the degree of brain atrophy correlates with disease onset and progression, as well as with CAG repeat length, the severity of associated symptoms, and global functioning (Brooks & Andrews, 2002). For better visualization, the following Figure 4 presents a comparison between a healthy control and a HD patient on MRI.

Figure 4. MRI differences between a healthy individual and a patient with HD



Note: The two MRI images are presented in the coronal view of T1-weighted scans, where A represents the brain of a healthy individual and B displays the brain of a patient with HD at Stage 2 of the disease. In comparison to the control subject (A), the HD patient (B) exhibits thinning of the putamen, indicated by the black arrow, and the caudate nucleus, pointed out by the white arrow (Mascalchi, et al., 2004). Moreover, the MRI scan of the HD patient (B) demonstrates evident global brain atrohy with an enlarged intraventricular space.

Another important aspect related to HD is metabolic activity, which provides information about neuronal functionality and synaptic efficiency (Niccolini & Politis, 2014). The main finding among HD patients is glucose hypometabolism in cortical and subcortical structures, likely reflecting disrupted intracellular functioning (Paulsen, 2009; Wilson & Politis, 2018). In contrast, increased glucose metabolism in the thalamus, occipital lobe, and cerebellum has been associated with abnormal glycolytic processes and/or insufficient inhibitory mechanisms (Wilson & Politis, 2018). Moreover, reduced metabolic activity is present prior to neural degeneration and the onset of symptoms, making it one of the earliest detectable changes in HD (Niccolini & Politis, 2014; Wilson & Politis, 2018). Nevertheless, hypometabolism may contribute to disease onset as differences among patients are independent of their CAG repeat length (Wilson & Politis, 2018). Comparatively, glucose metabolism shows a slower annual decline than the binding ability of dopamine receptors in the striatum, making it a less sensitive measure of disease progression (Niccolini & Politis, 2014; Wilson & Politis, 2018). However, cortical hypometabolism in the initial stages of HD has been correlated with a more aggressive rate of progression (Niccolini & Politis, 2014).

Motor abnormalities in HD have been associated with greater putamen atrophy, decreased PDE10A expression, and disrupted glucose metabolism in the striatum (Niccolini & Politis, 2014; Niccolini et al., 2015). Specifically, decreased cortical volume in the frontal areas is more pronounced in patients with bradykinesia compared to those with chorea (Niccolini & Politis, 2014). Additionally, bradykinetic patients also exhibit lower striatal dopamine receptors binding than choreatic individuals, suggesting this could be a potential differentiating factor among HD phenotypes (Niccolini & Politis, 2014; Wilson & Politis, 2018).

In contrast, cognitive impairments were correlated with putamen atrophy, as well as overall dopaminergic and metabolic abnormalities in cortical areas (Niccolini & Politis, 2014). Specifically, caudate atrophy was linked to attentional deficits (Craufurd & Snowden, 2002) while decreased cortical volume in the frontal areas was associated with memory decline (Wilson et al., 2018). Executive dysfunction was found to reflect frontal atrophy, along with reduced density of dopamine D_1 and D_2 receptors (Craufurd & Snowden, 2002). Furthermore, neurodegeneration of the corticostriatal pathway also contributes to disrupted social cognition, particularly emotional processing (Wilson et al., 2018).

Finally, psychiatric symptoms are commonly linked to corticostriatal atrophy (Wilson et al., 2018). The most frequent behavioral abnormality, apathy, is correlated with reduced gray matter volume and abnormal metabolic activity in frontal cortical regions, primarily the anterior cingulate cortex, dorsal anterior cingulate cortex, and insula, as well as in subcortical areas, particularly the ventral and dorsal striatum, amygdala, and hippocampus (Morris et al., 2022). Additionally, thalamic atrophy has been found to increase the probability of developing apathy, while atrophy of the middle cingulate cortex predicts the severity of these symptoms over time (Morris et al., 2022; Wilson et al., 2018). Mood regulation involves the limbic system, which sends information to the dorsomedial striatum, another early affected region in HD, potentially explaining why mood disorders are present in the initial stages of the disease (Anderson & Marder, 2001). One of the early disorders is depression, which is related to neuronal loss in the caudate nucleus (Anderson & Marder, 2001; Craufurd & Snowden, 2002). Consistently with findings in depressed individuals, HD patients exhibit glucose hypometabolism, primarily in the orbitofrontal cortex and inferior prefrontal cortex (Rosenblatt, 2007). Similarly, obsessive and compulsive symptoms share underlying neuropathology with patients suffering from obsessive-compulsive disorder, including decreased striatal volume and deteriorated

corticostriatal circuitry (Anderson et al., 2010). Decreased metabolic activity in frontal regions, along with pathology in the subcortical-limbic area, may contribute to the manifestation of psychotic symptoms (Anderson & Marshall, 2005). Moreover, REM sleep relies heavily on brainstem integrity, therefore, its deterioration may lead to sleep disturbances (Herzeg-Krzywoszanska & Krzywoszanski, 2019). Furthermore, irritability is also a result of disruption in the corticostriatal pathway, particularly involving connections between the orbitofrontal cortex and the ventral striatum of the basal ganglia (Anderson & Marshall, 2005).

Overall, the main neuropathological feature associated with HD is striatal atrophy (Bogaard et al., 2011) along with degeneration in the lentiform nucleus (Goh et al., 2018; Hewitt, 1961). Furthermore, neuroimaging evidence enhances our undersanding of the various clinical manifestations present in HD (Craufurd & Snowden, 2002).

2 METHODS

2.1 Objectives

The experimental part of the thesis focused on investigating the clinical profiles of HD patients, with particular emphasis on the phenotypic variability observed at disease onset. The **primary aim** was to examine clinical variabilities among different HD stages, defined according to the diagnostic criteria proposed by Reilmann et al. (2014): presymptomatic, prodromal, and manifest. Therefore, our research questions centered on investigating differences in demographic, motor, cognitive, behavioral (including functional), and neuroimaging evidence among the three stages. Specifically:

What are the differences in demographic distribution among the HD stages?

What are the differences in motor symptoms among the HD stages?

What are the differences in the degree of functionality among the HD stages?

How sensitivite are global cognitive screening tools in differentiating among the HD stages?

What are the structural brain differences among the HD stages?

What are the differences in cognitive symptoms among the HD stages?

What are the differences in behavioral symptoms among the HD stages?

The **secondary aim** of our thesis was to explore two main HD phenotypes: cognitive, psychiatric/behavioral, cognitive and psychiatric/behavioral, all either with or without motor onset. This was further investigated through our research questions, which focused on differences in onset prevalence and discrepancies in motor, cognitive, behavioral, functional, genetic, and neuroimaiging evidence between the two phenotypes. In particular:

What are the differences in motor symptoms between HD phenotypes?

What are the differences in the degree of functionality between HD phenotypes?

What are the structural brain differences between HD phenotypes?

What are the differences in the CAG repeat expansion between HD phenotypes?

What are the differences in cognitive symptoms between HD phenotypes?

What are the differences in behavioral symptoms between HD phenotypes?

What are the differences in onset prevalence between HD phenotypes?

2.2 Materials and methods

We conducted a retrospecive, cross-sectional observational study. We analyzed the medical records of genetically determined HD followed at Movement Disorders Clinic at the Department of Neuroscience of the Padua University Hospital. Patients were followed at the clinic for over 12 years, from 2012 to 2024. Relevant information regarding comprehensive clinical, motor, behavioral, and neuropsychological evaluations from their respective protocols, as well as neuroimaging evidence from radiological reporst, was extracted.

2.3 Participants

The research population comprised a total of 45 participants admitted to the Padua University Hospital. All participants met the inclusion criteria of an HD diagnosis, confirmed by a positive genetic test. Additionally, these participants underwent a thorough neurological and neuropsychological examination, as well as a neuroimaging evaluation using MRI.

All 45 participants were eligible to be included in investigating our first research aim, which focused on the differences across various stages. This group of 45 individuals thus constituted our first research sample.

For the investigative purposes of our second research aim, which addresses the characterization of different HD phenotypes, we applied additional selection criteria. Specifically, we excluded six participants: two individuals were excluded due to a lack of clinical information regarding the onset of their initial symptoms, and four participants were excluded due to the total absence of symptoms. Consequently, our second research sample consisted of 39 participants who met all criteria for this phenotype-based investigation.

2.4 Motor evaluation

The motor assessment was conducted as a part of a neurological examination, with experts neurologists who have been certified for administering the motor section of the ***"Unified Huntington's Disease Rating Scale – UHDRS"*** (Huntington Study Group,

1996). The motor assessment includes evaluating oculomotor function (6 items), chorea (7 items), dystonia (5 items), bradykinesia (11 items) and rigidity (2 items). The sum of the various items corresponds to a total score called TMS (total motor score), which provides an estimate of the degree of motor disability of the individual patient. The higher the TMS value, the greater the patient's motor disability, with a range from a minimum of 0 to a maximum of 124 points.

2.5 Neuropsychological evaluation

Cognitive functioning was evaluated with a comprehensive battery of neuropsychological tests measuring six cognitive domains: executive functioning, attention, visuospatial abilities, memory, language, and social cognition. This included two global screening tools, the ***"Montreal Cognitive Assessment – MoCA"*** (Santangelo et al., 2015) and the ***"Mini-Mental State Examination – MMSE"*** (Magni et al., 1996), both of which assess general cognitive abilities.

The ***"MMSE"*** (Magni et al., 1996) is broadly used to assess cognitive deterioration across six main cognitive domains: orientation in time and space, word recall, attention, working memory, language (including naming, repetition, comprehension, and writing), and visuospatial skills. The maximum score of this test is 30 points, with a cut-off for mild cognitive impairment (MCI) below 24 points.

Similarly, the ***"MoCA"*** (Santangelo et al., 2015) is a widely used screening tool for evaluating cognitive impairment, with higher sensitivity than the MMSE. More specfically, the MoCA uses 30-point scale, with a cut-off score below 26 to assess seven cognitive domains: visuospatial/executive skills, naming, memory (both immediate and delayed recall), attention, language, abstraction, and orientation.

Afterwards, a detailed evaluation of each of the six general cognitive domain – executive functions, attention, visuospatial skills, memory, language, and social cognition – was provided. Specifically, executive functioning was assessed using Phonemic Fluency (Costa et al., 2014) and the Stroop Test (Caffarra et al., 2002a). The ***"Phonemic Fluency"*** (Costa et al., 2014) is a test of verbal capacity where the individual is asked to produce as many words as possible starting with a given letter (e.g., F, A, S) in 60 seconds. Additionally, this task places high demands on working memory, cognitive flexibility, and inhibition, all of which reflect frontal lobe functioning.

The ***"Stroop Test"*** (Caffarra et al., 2002a) is used to assess goal-oriented behavior, working memory, and inhibition through three different tasks. The first two tasks are under congruous conditions, where the individual is asked to read names of the colors in black ink and to name the color of presented patches. In contrast, during the third task, the individual is required to name the ink color that is inconsistent with the word color, for instance, the word "blue" may be presented in red ink (Scarpina & Tagini, 2017).

The attention domain was explored through the oral version of SDMT (Nocentini, et al., 2006), TMT-A and TMT-B (Giovagnoli et al., 1996), and Alternate Fluency (Costa et al., 2014). The oral version of the ***"SDMT"*** (Nocentini, et al., 2006) measures sustained attention and processing speed. This task involves nine symbols, each associated with a number from 1 to 9. Individuals are instructed to verbally match the symbols to their corresponding numbers as accurately and quickly as possible within a span of 90 seconds (Smith, 1973).

The ***"TMT-A and TMT-B"*** (Giovagnoli et al., 1996) are two different measurement tools assessing processing speed and attention. In particular, the TMT-A measures sustained attention by requiring individuals to to connect a sequence of numbered circles in the correct asceding order, while focusing on accuracy and speed. In contrast, the TMT-B assesses divided attention by presenting both numbers and letters, arranged in circles. The main goal is to alternate between connecting numbers in ascending order and letters in alphabetical order. Additionally, the alternating task in TMT-B challenges individual's set-shifting ability as well as cognitive flexibility.

The ***"Alternate Fluency"*** test (Costa et al., 2014), similar to Phonemic Fluency, assesses verbal abilities within 60 seconds. However, instead of generating words starting with a predefined letter, individuals are asked to produce pairs of words – one starting with a specific letter and the other belonging to a designated category. More specifically, this task measures attentional and set-shifting abilities, along with cognitive flexibility, which reflects frontal lobe functioning.

Visuospatial abilities were assessed using three cognitive tests: the Benton JoLO (Benton, 1994), the VOSP (Warrington & James, 1991), and the ROCF-copy (Caffarra et al., 2002b). The ***"Benton JoLO"*** (Benton, 1994) evaluates the ability to perceive spatial orientation of lines, useful in subcortical dementias. The test consists of two forms, Form H and Form V, each containing 30 items and a model with 11 semicircularly arranged lines. During the task, individuals are shown two unnumbered lines and asked to match them to

the corresponding numbered lines in the model. The difference between the forms lies in the line length – the Form V uses shorter lines, therefore, advancing difficulty.

The second ***"VOSP"*** battery (Warrington & James, 1991) consists of eight components designed to evaluate specific aspects of visual perception related to object and space. To assess object perception, which relates to the functioning of the ventral stream, the battery includes four tasks such as incomplete letters. For evaluating space recognition, associated with the dorsal stream, four tasks like dot counting are used. Each subtest comprises either 10, 20 or 30 items.

Thirdly, the ***"ROCF-copy"*** (Caffarra et al., 2002b) was utilized to assess visuoconstructional abilities, planning and organizational skills, problem-solving strategies, as well as perceptuo-motor functioning. In this task, individuals are asked to redraw a bidimensional figure as quickly and accurately as possible. This figure consists of a complex combination of various geometric shapes, which are particularly challenging for patients with HD due their disrupted reproduction strategies.

Another domain of interest was memory, investigated through four neuropsychological tests: the ROCF-recall (Caffarra et al., 2002b), the BSRT (Spinnler & Tognoni, 1987), the VPA test (Wechsler, 1945), and the HVLT (Brandt, 1991). The ***"ROCF-recall"*** (Caffarra et al., 2002b) is a continuation of the previously mentioned ROCF-copy. In this task, visuoperceptual memory is assessed by asking the individual to recall the complex two-dimensional figure composed of assorted geometrical patterns after 15-minute delay from its initial copy.

The main aim of the next verbal memory test, ***"BSRT"*** (Spinnler & Tognoni, 1987), is to evaluate ability recall verbal information both immediately and after a delay. The individual listens to a short story and is asked to retell it as accurately as possible immediately after hearing it. Then, after 20 minutes, they are asked to recall the story again with as many details as possible. The total score for this test is 16, with 8 points allocated for both, immediate and delayed recall (Del Signore et al., 2023).

The ***"VPA"*** (Wechsler, 1945) is an episodic memory test found within the Wechsler Memory Scale. During the task, individuals listen to 10 word pairs, some of which are easily associated, while others are harder to logically pair. These are presented in three distinct slots. The main task involves using an association strategy to successfully encode the word pairs. This is tested by presenting only one word from each pair, aand the individual is required to provide the other associated word.

Finally, ***"HVLT"*** (Brandt, 1991) is used for assessing memory and verbal learning ability through a list of 12 words. This list is read to the individual during three successive learning trials, each followed by an immediate recall task. The fourth trial consists of a delayed recall of the learned words. If the individual fails the delayed recall, a delayed recognition task follows, in which they are presented with a list of 24 words and must indicate "yes" or "no" to whether they believe each word was part of the original list.

The next domain, language, was assessed using tasks such as the BNT (Kaplan et al., 1983) and Semantic Fluency (Costa et al., 2014). The ***"BNT"*** (Kaplan et al., 1983) is a test of confrontational naming, evaluating language abilities. It contains 60 items, represented by various drawn pictures, progressing from easy items, such as a house, to more difficult ones, like a palette. If the individual fails to name an item correctly, they are provided with a semantic cue, followed by a phonemic cue if necessary.

The ***"Semantic Fluency"*** test (Costa et al., 2014) is the third of the verbal fluency tests. Similarly to the previously mentioned Phonemic Fluency and Alternate Fluency tasks, the individual is required to generate as many words as possible within 60 seconds. However, in this task, the words must belong to a specific category defined by the examiner (e.g. animals, fruits, colors). Additionally, this task places high demands on lexical retrieval, vocabulary use, and semantic knowledge (Gordon et al., 2018).

Lastly, social cognition was measured through the RMET (Baron-Cohen et al., 1997; Baron-Cohen et al., 2001), the SET (Dodich et al., 2015), and the FACE Test (Terruzzi et al., 2023). The ***"RMET"*** (Baron-Cohen et al., 1997; Baron-Cohen et al., 2001) assesses empathy and Theory of Mind through 25 images of the eye region. The individual is asked to choose one of four emotions that best represents the feeling of the person in the picture. The main purpose of this test is to evaluate the individual's ability to attribute mental states to others, or a process known as mentalising, which is essential for predicting others' behaviors.

The ***"SET"*** (Dodich et al., 2015) is a non-verbal test that evaluates two primry skills: identifying others' intentions and inferring their emotions. During the task, the individual analyzes three pictures that together form a story and must correctly determine the story's ending. The tasks contains a set of six stories, with one point assigned for each correct answer, allowing for a maximum score of 18 points. One of the tasks represents a control condition involving causality.

The final cognitive test in the neuropsychological protocol was the ***"FACE Test"*** (Terruzzi et al., 2023), which measures the ability to recognize others' mental states in a

complex manner based on their facial expression. The task consists of 36 pictures of individuals displaying various facial expressions. The individual is asked to select one of four descriptions that best matches the presented picture. The maximum possible score is 36, with one point awarded for each correct answer.

2.6 Behavioral evaluation

The **behavioral profile** was assessed using the behavioral part of the ***"UHDRS"*** (Huntington Study Group, 1996). The behavioral assessment focuses on psychiatric disturbances, specifically depression, low self-esteem, anxiety, suicidal ideations, aggression, irritability, obsessions, compulsions, delirium, hallucinations, and apathy. Each item is rated for severity on a 5-point Likert scale ranging from 0 (absent) to 4 (severe), and for frequency, also on a 5-point Likert scale from 0 (absent) to 4 (almost always).

2.7 Functional assessment

To investigate the functional independence of patients, we used th functional assessments present in the ***"UHDRS"*** (Huntington Study Group, 1996). It includes three measures: a) the ***"Total Functional Capacity – TFC"*** consists of five Likert-scale items related to occupation, finances, household chores, activities of daily living, and care requirements, with a maximum score of 13; b) the ***"Independence Scale – IS"*** evaluates the individual's level of independence, ranging from 10 (bedridden and with internal nutrition) to 100 (total independence); and c) the ***"Functional Assessment – FAS"*** comprising of 25 items, scored with "yes" or "no" response, that measure the individual's capability to perform specific daily tasks.

2.8 Neuroradiological evaluation

The neuroimaging data were collected during the neuroradiological evaluation conducted at the Department of Nuclear Medicine of the Padua University Hospital. More specifically, the MRI was performed as part of a combined PET-MRI examination to explore HD pathology-related structural brain changes. Four distinct sequences were used

for the acquisition of MRI images: T1- and T2-weighted sequences, Fluid-Attenuated Inversion Recovery (FLAIR) sequences, and Susceptibility-Weighted Imaging (SWI) sequences.

The analysis of the images was conducted using a "whole brain" technique, allowing for a comprehensive assessment of the entire brain tissue without focusing on specific regions. Specifically, we employed voxel-based morphometry (VBM), an automated software method that enabled us to measure and compare local concentrations of different brain tissues across participants.

Our MRI data processing initially involved segmenting the image data. Using specific software, after excluding cranial tissue and soft tissues, we divided images into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). The segmentation was performed by the software based on the intensity and spatial distribution of the voxels. Subsequently, a normalization process was carried out to standardize anatomical and dimensional differences. The images were partially transformed to be placed into a unique reference space, specifically the Montreal Neurological Institute (MNI) space, which is one of the most commonly used standard spaces.

For our study, the images were processed with BAAD v4.3, a software integrated with the statistical parametric mapping tool SPM12. This software also includes a computational anatomy toolbox (CAT12), which was used for the diffeomorphic segmentation of the 3D T1-weighted images after bias correction, quality control assessment, and intracranial volume estimation. FLAIR-T2-weighted sequences were included in the multimodal segmentation to correct for the estimation of brain atrophy due to the presence of white matter lesions, thereby improving the segmentation of subcortical structures.

Finally, normalization to the standard MNI space was performed through the CAT12 tool integrated into BAAD. Deformation maps for each subject's GM (VBM-GM) and WM (VBM-WM) were then obtained using an MNI atlas mask: specifically, GM – T1 (35% threshold) and MNI-Fractional Anisotropy for WM with a 25% threshold to avoid the incorrect assignment of tissue to GM or WM.

2.9 Data analysis

2.9.1 Clinical, motor, behavioral and neuropsychological data analysis

In the initial analytic stages, we utilized Microsoft Excel to organize all available data. The final dataset was then imported into the statistical program R (version 4.4.1), which allowed us to perform statistical analysis using various statistical tests.

For the first research sample, our data did not follow a normal distribution. Therefore, we employed a non-parametric Kruskal-Wallis test (H test). Subsequently, we used descriptive stastics to obtain measures of central tendency, specifically median (Md), and measures of dispersion, particularly the interquartile range (IRQ) representing the 25^{th} and 75^{th} percentiles. Additionally, post hoc comparisons were performed to investigate the direction of significance between the independent groups – presymptomatic, prodromal, and manifest. The cognitive tests were analysed using *z-compound* scores for each cognitive domain – executive functions, attention, visuospatial skills, memory, language, and social cognition. Nonetheless, the chi-square test (χ^2) of independence was used to compare categorical variables.

Regarding the second research aim, the data similarly did not follow a normal distribution. Thus, we used a non-parametric Mann Whitney test (U test). As in the previous analysis, we employed descriptive stastics to obtain measures of central tendency (Md) and measures of dispersion (IRQ between the 25^{th} and 75^{th} percentiles). Furthermore, we used the non-parametric Fisher's exact test (FET test) to compare categorical variable.

2.9.2 Neuroimaging analysis

To identify patterns of cortical and subcortical alterations in each subject with HD, the VBM-GM and VBM-WM data of each patient were compared with healthy subjects of the same age and sex, derived from the ADNI (Alzheimer's Disease Neuroimaging Initiative) dataset included in the BAAD software. The ADNI dataset comprises a collection of MRI images from healthy individuals that can serve as controls for various studies. The BAAD software automatically selects the most appropriate number and characteristics of controls for the analysis, paying attention to various parameters such as gender and age.

The comparison between diseased subjects and controls was performed through a non-parametric analysis using the Statistical NonParametric Maping tool, SnPM12. The resulting T-statistic maps were included in a second-level T-test analysis for both GM and WM. The threshold-free cluster enhancement (TFCE), a non-parametric method optimal for cluster threshold estimation based on 5000 LOOP iterations, was applied to the obtained maps, with corrections for multiple comparisons at family-wise error (FEW) $p<0.001$.

The resulting maps were overlaid on a 3D reconstruction of the standard template in MNI space. The localization of GM activation clusters was defined based on the atlas provided with the automated anatomical parcellation tool AAL 3.1, while the JHU White-Matter Tractography Atlas was used to identify WM tracts.

3 RESULTS

Our first research sample included 45 participants divided into three stages: the presymptomatic group consisted of 4 participants (75.0% female), the prodromal group of 12 participants (60.0% female), and the manifest group of 29 participants (55.6% female) (see Table 1).

The median age at assessment was 42.0 years (IRQ_{25-75} = 35.5 – 47.5) for the presymptomatic group, 46.0 years (IRQ_{25-75} = 41.5 – 54.5) for the prodromal group, and 53.0 years (IRQ_{25-75} = 45.8 – 61.0) for the manifest group, showing a linear but non-significant trend (p = .065). The median disease duration from onset was 4.0 years (IRQ_{25-75} = 4.0 – 4.0) in the presymptomatic group, 5.5 years (IRQ_{25-75} = 4.0 – 10.0) in the prodromal group, and 9.0 years (IRQ_{25-75} = 6.0 – 12.0) in the manifest group, also indicating a linear but non-significant trend (p = .082). Morphological changes in GM and WM were expressed using a T-score, although we did not find any significant difference.

The median length of the CAG repeat did not differ across all groups, with medians of 41.0 for the first group, and 43.0 for both the second and third groups (p = 0.107). Approximately one-third of participants in the prodromal and manifest group had a CAG expansion equal to or greater than 44 (p = 0.431) (see Table 1).

We observed a statistically significant difference for the overall severity of motor symptoms (TMS) across the stages [(group 1, Md = 0.0 IRQ_{25-75} = 0.0 – 3.0; group 2, Md = 12.0 IRQ_{25-75} = 10.0 – 25.0; group 3, Md = 37.0 IRQ_{25-75} = 27.0 – 56.0) p < .001]. The same significant trend was observed in specific motor components of UHDRS, namely rigidity [(group 1, Md = 0.0 IRQ_{25-75} = 0.0 – 3.0; group 2, Md = 5.0 IRQ_{25-75} = 0.0 – 6.0; group 3, Md = 8.0 IRQ_{25-75} = 4.0 – 11.8) p = .019]; and chorea [(group 1, Md = 0.0 IRQ_{25-75} = 0.0 – 0.0; group 2, Md = 7.0 IRQ_{25-75} = 3.0 – 9.0; group 3, Md = 12.0 IRQ_{25-75} = 7.3 – 18.3) p < .005] (see Table 1).

Table 1. Demographic and clinical differences across HD stages

	Presymptomatic (1) n = 4		Prodromal (2) n = 12		Manifest (3) n = 29		H	1 x 2	1 x 3	2 x 3
	Md	IRQ 25 –75	Md	IRQ 25 –75	Md	IRQ 25 – 75	P			
Age at visit	42.0	35.5 – 47.5	46.0	41.5 – 54.5	53.0	45.8 – 61.0	.065			
Sex (%F)	75.0%		60.0%		55.6%		.773			
Age of onset	45.0	45.0 – 45.0	44.0	36.0 – 51.0	48.0	36.5 – 56.8	.729			
Disease duration (from onset)	4.0	4.0 – 4.0	5.5	4.0 – 10.0	9.0	6.0 – 12.0	.082			
Disease duration	4.0	4.0 – 4.0	4.0	3.0 – 7.0	6.0	3.75 – 10.0	.311			
Education	13.0	12.5 – 15.0	13.0	11.0 – 13.0	13.0	8.0 – 13.0	.362			
UHDRS (motor-new)	0.0	0.0 – 3.0	12.0	10.0 – 25.0	37.0	27.0 – 56.0	< .001		*	*
UHDRS (rigidity)	0.0	0.0 – 3.0	5.0	0.0 – 6.0	8.0	4.0 – 11.8	.019		*	*
UHDRS (chorea)	0.0	0.0 – 0.0	7.0	3.0 – 9.0	12.0	7.3 – 18.3	.005		*	*
UHDRS (FAS)	25.0	24.5 – 25.0	24.0	23.0 – 24.5	18.0	11.5 – 21.3	< .001		*	*
UHDRS (TCF)	13.0	13.0 – 13.0	13.0	12.0 – 13.0	8.0	5.0 – 11.0	< .001		*	*
UHDRS (IS)	100.0	100.0 – 100.0	100.0	95.0 – 100.0	75.0	60.0 – 85.0	< .001		*	*
UHDRS (behav)	2.5	0.0 – 5.5	3.0	0.0 – 13.5	4.0	0.0 – 16.3	.525			
MMSE corr	25.2	24.6 – 25.7	25.2	24.2 – 26.6	23.0	18.2 – 25.2	.009			*
MoCA corr	25.7	22.8 – 26.2	19.5	18.3 – 24.0	16.1	13.2 – 20.6	.007		*	*
GM atrophy (T score)	1.1	0.7 – 1.2	0.6	0.4 – 1.0	0.4	-0.1 – 0.8	.179			
WM atrophy (T score)	1.7	1.5 – 1.7	0.9	0.6 – 1.6	0.4	-0.4 – 1.6	.294			
CAG triplets expansion	41.0	39.0 – 42.0	43.0	41.0 – 44.0	43.0	41.8 – 45.0	.107			
≥ 44 CAG (%)	0.0%		30.0%		31.2%		.431			

*Note: Table 1 shows the main demographic and clinical differences between presymptomatic, prodromal, and manifest groups. The clinical differences are depicted through the motor component of UHDRS, including rigidity and chorea; the functional component of UHDRS, covering all three scales (FAS, TCF, and IS); the overall scores of the behavioral component of UHDRS; two screening tools, MMSE and MoCA; neuroimaging findings; and genetic results. Abbreviations: Md = median, IRQ = interquartile range, H = Kruskal-Wallis test, p = p-value, * = p <.005.*

Our results displayed a statistically significant difference across all HD stages, suggesting a decline in functionality over time. This trend was observed among all three functional scales, in particular, FAS [(group 1, Md = 25.0 IRQ_{25-75} = 24.5 – 25.0; group 2, Md = 24.0 IRQ_{25-75} = 23.0 – 24.5; group 3, Md = 18.0 IRQ_{25-75} = 11.5 – 21.3) $p < .001$]; TCF [(group 1, Md = 13.0 IRQ_{25-75} = 13.0 – 13.0; group 2, Md = 13.0 IRQ_{25-75} = 12.0 – 13.0; group 3, Md = 8.0 IRQ_{25-75} = 5.0 – 11.0) $p < .001$]; and IS [(group 1, Md = 100.0 IRQ_{25-75} = 100.0 – 100.0; group 2, Md = 100.0 IRQ_{25-75} = 95.0 – 100.0; group 3, Md = 75.0 IRQ_{25-75} = 60.0 – 85.0) $p < .001$]. Post-hoc analysis showed significant differences between the presymptomatic and manifest groups, as well as between the prodromal and manifest groups, but not between the presymptomatic and prodromal groups (see Table 1).

Concerning global cognitive performance (see Table 1), we found a difference in the MMSE scores [group 1: Md = 25.2 (IRQ_{25-75} = 24.6 – 25.7); group 2: Md = 25.2 (IRQ_{25-75} = 24.2 – 26.6); group 3: Md = 23.0 (IRQ_{25-75} = 18.2 – 25.2) $p = .009$], with statistical significance found between group 1 and 3; as well as in the MoCA scores [group 1: Md = 25.7 (IRQ_{25-75} = 22.8 – 26.2); group 2: Md = 19.5 (IRQ_{25-75} = 18.3 – 24.0); group 3: Md = 16.1 (IRQ_{25-75} = 13.2 – 20.6) $p = .007$]. Post-hoc analysis showed significant differences between groups 1 and 3, and between groups 2 and 3, but not between groups 1 and 2. Thus, both MMSE and MoCA appear senstive in distinguishing between the prodromal and manifest stages, with MoCA also sensitive in capturing differences between the presymptomatic and manifest stages.

With regard to the cognitive profile, statistically significant differences were found in all domains across the three groups (see Table 2). In particular, we found a statistically significant difference in executive functioning [(group 1, Md = 0.5 IRQ_{25-75} = 0.3 – 0.8; group 2, Md = -0.2 IRQ_{25-75} = -0.3 – 0.1; group 3, Md = -1.2 IRQ_{25-75} = -2.2 – -0.8) $p < .001$], and post-hoc comparison revealed statistically significant difference between groups 1 and 3, and between groups 2 and 3, but not between groups 1 and 2. We also found a statistically significant difference in the attention [(group 1, Md = 0.4 IRQ_{25-75} = 0.2 – 0.6; group 2, Md = -0.5 IRQ_{25-75} = -1.8 – 0.0; group 3, Md = -2.1 IRQ_{25-75} = -3.3 – -1.0) $p < .001$], with post-hoc analysis showing statistically significant difference between the groups 1 and 2, between the groups 1 and 3, as well as between the groups 2 and 3. Statistically significant differences was also found for the visuospatial skills [(group 1, Md = 0.4 IRQ_{25-75} = -0.1 – 0.8; group 2, Md = -0.3 IRQ_{25-75} = -1.0 – 0.3; group 3, Md = -1.0 IRQ_{25-75} = -4.0 – -0.5) $p = .012$]. Post-hoc analysis revealed statistically significant difference between the groups 1 and 3, as well as between the groups 2 and 3.For the

memory domain we found statistically significant difference as well [(group 1, Md = -0.7 IRQ_{25-75} = -1.3 – -0.2; group 2, Md = -2.1 IRQ_{25-75} = -2.1 – 1.3; group 3, Md = -2.7 IRQ_{25-75} = -3.3 – -2.3) p = .005], with post-hoc comparion revealing statistically significant difference between the groups 1 and 3, as well as between the groups 2 and 3. Additionally, we found statistically significant difference in the language domain [(group 1, Md = -0.9 IRQ_{25-75} = -0.6 – 11323.5; group 2, Md = -0.9 IRQ_{25-75} = -2.5 – -0.1; group 3, Md = -2.1 IRQ_{25-75} = -3.0 – -1.5) p < .001] and post-hoc analysis showed statistically significant difference between the groups 1 and 3, and between the groups 2 and 3. Lastly, statistically significant difference was also found for the social cognition domain [(group 1, Md = -0.1> IRQ_{25-75} = -0.1 – 0.1; group 2, Md = -1.2 IRQ_{25-75} = -1.7 – 0.5; group 3, Md = -1.3 IRQ_{25-75} = -2.3 – -0.5) p = .030]. Post-hoc analysis revealed statistically significant difference between the groups 1 and 2, and 1 and 3. Moreover, when considering the clinical meaning of cognitive performance across HD stages, none of the presymptomatic patients exhibited pathological performance (defined as a *z-score* of -1.5 below the mean of the healthy population). Only memory showed a clinically significant alteration in the prodromal group, while further alterations in attention and language were observed in the manifest group. Executive, visuospatial, and social cognition abilities significantly decreased across stages, although they did not reach the level of pathological performance.

Table 2. Cognitive differences across the HD stages

	Presymptomatic (1) n = 4		**Prodromal (2) n = 12**		**Manifest (3) n = 29**		**H**	**1 x 2**	**1 x 3**	**2 x 3**
	Md	**IRQ 25-75**	**Md**	**IRQ 25-75**	**Md**	**IRQ 25-75**	**P**			
Executive z-compound	0.5	0.3 – 0.8	-0.2	-0.3 – 0.1	-1.2	-2.2 – -0.8	<.001		*	*
Attention z-compound	0.4	0.2 – 0.6	-0.5	-1.8 – 0.0	-2.1	-3.3 – -1.0	<.001	*	*	*
Visuospatial z-compound	0.4	-0.1 – 0.8	-0.3	-1.0 – 0.3	-1.0	-4.0 – -0.5	.012		*	*
Memory z-compound	-0.7	-1.3 – -0.2	-2.1	-2.1 – -1.3	-2.7	-3.3 – -2.3	.005		*	*
Language z-compound	-0.9	-0.6 – 11323.5	-0.9	-2.5 – -0.1	-2.1	-3.0 – -1.5	<.001		*	*
Social cog. z-compound	-0.1>	-0.1 – 0.1	-1.2	-1.7 – -0.5	-1.3	-2.3 – -0.5	.030	*	*	

*Note: Table 2 outlines the differences in cognitive profiles between the presymptomatic, prodromal, and manifest groups across six cognitive domains: executive functioning, attention, visuospatial skills, memory, language, and social cognition. Abbreviations: Md = median, IRQ = interquartile range, H = Kruskal-Wallis test, p = p-value, * = p <.005.*

Behavioural differences were captured through the behavioral component of the UHDRS. There were no significant differences across the three stages in the overall score (see Table 1) or for each specific symptom (see Table 3). However, depression and low self-esteem/guilt showed a linear increase, reflecting increasing severity over time. Anxiety was present across all three stages but was highest in the presymptomatic stage (75.0%), suggesting a decrease of the anxiety symptoms as the disease progresses. Suicidal ideations/thoughs were present, with higher prevalence in the presymptomatic and manifest stages, but were entirely absent in the prodromal stage. Aggression and irritability became more prevalent over time, while obsessions and compulsions with a peak in the prodromal stage. Delirium and hallucinations were also rare and appeared only in the most advanced stage.

Table 3. Behavioral differences across HD stages

	Presymptomatic (1) n = 4	**Prodromal (2) n = 12**	**Manifest (3) n = 29**	**(χ^2)**
	Percentage	**Percentage**	**Percentage**	**P**
Depression	25.0%	50.0%	58.6%	.221
Low self-esteem/Guilt	0.0%	16.7%	20.7%	.352
Anxiety	75.0%	41.7%	44.8%	.445
Suicidal ideations/thoughts	25.0%	0.0%	17.2%	.654
Aggression	25.0%	33.3%	31.0%	.913
Irritability	0.0%	41.7%	31.0%	.546
Obsessions	0.0%	8.3%	3.4%	.902
Compulsions	0.0%	8.3%	0%	.389
Delirium	0.0%	0.0%	3.4%	.490
Hallucinations	0.0%	0.0%	3.4%	.490

Note: Table 3 displays the behavioral changes observed in the bUHDRS ascross different HD stages. Abbreviations: (χ^2) = chi-squared test, p = p-value.

Our second aim focused on investigating clinical differences in HD patients across various phenotypes. Specifically, we divided our participants into two major groups based on their initial symptoms: 1) those who did not exhibit motor symptoms but solely behavioral, cognitive, or both types of manifestations (Motor -; n = 13); and 2) those who presented with motor disturbances, either alone or in combination with behavioral, cognitive, or both types of symptoms (Motor +; n = 26) (see Tables 4-7).

No significant demographic differences were found (see Table 4). The median age at visit was marginally higher in Motor + (Md = 52.5, $IRQ_{25\text{-}75}$ = 44.0 – 57.0) than in

Motor - (Md = 50.0, IRQ_{25-75} = 43.1 – 55.5), p = .438; as well as the median age of onset [(Motor -, Md = 41.0 IRQ_{25-75} = 37.0 – 50.3; Motor +, Md = 49.0 IRQ_{25-75} = 35.8 – 56.3), p = .390]. The median years of education were comparable between groups (Md = 13.0, p = .910). Nonetheless, non-motor onset was more prevalent among women (76.9%), than motor onset (42.3%), though this difference did not reach statistical significance (p = .089).

Table 4. Demographic and clinical differences between HD phenotypes

	Motor - (Behav | Cog | Behav + Cog) n = 13		**Motor + (Behav | Cog | Behav + Cog) n = 26**		**U**
	Md	**IRQ 25 –75**	**Md**	**IRQ 25 –75**	**P**
Age at visit	50.0	43.1 – 55.5	52.5	44.0 – 57.0	.438
Sex (%F)	76.9%		42.3%		.089
Age of onset	41.0	37.0 – 50.3	49.0	35.8 – 56.3	.390
Disease duration	7.0	2.5 – 10.0	5.0	3.8 – 7.0	.809
Education	13.0	9.8 – 13.0	13.0	8.8 – 13.0	.910
UHDRS (motor-new)	20.5	7.0 – 28.0	36.0	24.5 – 52.0	.013*
UHDRS (rigidity)	5.0	3.0 – 6.5	7.0	3.3 – 10.0	.239
UHDRS (chorea)	3.0	0.0 – 8.3	12.0	7.3 – 18.3	.014*
UHDRS (FAS)	22.5	21.0 – 24.5	18.5	13.0 – 22.5	.029*
UHDRS (TCF)	12.0	10.0 – 13.0	9.0	5.5 – 12.0	.094
UHDRS (IS)	87.5	80.0 – 100.0	85.0	61.3 – 93.8	.058
UHDRS (behav)	6.0	0.0 – 10.3	4.0	0.0 – 17.0	.833
MMSE corr	24.2	21.5 – 26.1	24.0	18.8 – 25.2	.632
MoCA corr	18.0	14.3 – 21.0	18.8	13.6 – 21.1	.861
GM atrophy (T score)	0.6	0.3 – 0.8	0.6	0.1 – 1.2	.777
WM atrophy (T score)	0.6	0.3 – 1.0	1.2	0.4 – 1.8	.396
CAG triplets expansion	43.0	41.5 – 44.0	43.0	40.5 – 45.5	.933
≥ 44 CAG (%)	41.7%		37.5%		.904
MDs stages					
Premanifest (%)	8%		8%		
Prodromal (%)	31%		27%		
Manifest (%)	62%		73%		
					.279

*Note: Table 4 shows the primary demographic and clinical differences between the two main HD phenotypes: those with initial motor manifestations (Motor +) and those without (Motor -). The clinical differences are presented using the following measures: the motor component of UHDRS, with a focus on two key symptoms (rigidity and chorea); the functional component of UHDRS, including all three scales (FAS, TCF, and IS); overall scores on the behavioral component of UHDRS; two screening tools MMSE and MoCA; neuroimaging findings; and genetic results. Abbreviations: Md = median, IRQ = interquartile range, U = Mann-Whitney test, p = p-value, * p < .05.*

Concerning motor differences between the two phenotypes, results showed a greater prevalence of motor symptoms in the Motor + group than in the Motor - group. Specifically, statistically significant differences were observed in the TMS score of UHDRS [(Motor -, Md = 20.5 IRQ_{25-75} = 7.0 – 28.0; Motor +, Md = 36.0 IRQ_{25-75} = 24.5 – 52.0), p = .013] and in chorea [(Motor -, Md = 3.0 IRQ_{25-75} = 0.0 – 8.3; Motor +, Md = 12.0 IRQ_{25-75} = 7.3 – 18.3), p = .014], whereas the difference in rigidity was not significant [(Motor -, Md = 5.0 IRQ_{25-75} = 3.0 – 6.5; Motor +, Md = 7.0 IRQ_{25-75} = 3.3 – 10.0), p = .239] (see Table 4).

The Motor - group demonstrated higher functionality across all three subscales, suggesting that motor symptoms may impact functional independence more than neuropsychiatric alterations. These results were statistically significant for FAS [(Motor -, Md = 22.5 IRQ_{25-75} = 21.0 – 24.5; Motor +, Md = 18.5 IRQ_{25-75} = 13.0 – 22.5), p = .029], but not for TCF [(Motor -, Md = 12.0 IRQ_{25-75} = 10.0 – 13.0; Motor +, Md = 9.0 IRQ_{25-75} = 5.5 – 12.0), p = .094]; or IS [(Motor -, Md = 87.5 IRQ_{25-75} = 80.0 – 100.0; Motor +, Md = 85.0 IRQ_{25-75} = 61.3 – 93.8), p = .058] (see Table 4).

Structural differences in GM and WM between the two groups are also presented in Table 4. No significant differences were found in GM atrophy [(Motor -, Md = 0.6 IRQ_{25-75} = 0.3 – 0.8; Motor +, Md = 0.6 IRQ_{25-75} = 0.1 – 1.2) p = .777] or in WM atrophy [(Motor -, Md = 0.6 IRQ_{25-75} = 0.3 – 1.0; Motor +, Md = 1.2 IRQ_{25-75} = 0.4 – 1.8) p = .396].

No significant differences between the two groups were observed in the CAG triplet expansion (see Table 4). More specifically, the median number of CAG triplets was consistent across HD phenotypes (Md = 43.0, p = .933). However, the percentage of participants with expansion equal or larger than 44 was modestly higher in those without initial motor symptoms in the Motor - group (41.7%) compared to those with them in the Motor + group (37.5%), p = .904.

When comparing cognitive profiles in the two phenotypes, we first analyzed corrected scores on the MMSE and MoCA (see Table 4). However, no significant differences were found, neither between the Motor - and Motor + group, nor between the sensitivity of the two scales. Similarly, no statistically significant differences were observed in specific cognitive domains (see Table 5), suggesting that motor symptoms do not affect global cognition or specific cognitive domains. Both the Motor – and the Motor + group displayed clinically significant cognitive deficits in attention [(Motor -, Md = -1.6 IRQ_{25-75} = -2.5 – -0.3; Motor +, Md = -1.9 IRQ_{25-75} = -3.1 – -0.6) p = .633], memory [(Motor -, Md = -2.3 IRQ_{25-75} = -2.8 – -1.9; Motor +, Md = -2.3 IRQ_{25-75} = -3.7 – -1.9) p =

.357], and language [(Motor -, Md = -2.1 IRQ_{25-75} = -2.5 – -1.5; Motor +, Md = -1.5 IRQ_{25-75} = -2.9 – -1.0) p = .323]. No significant deficits were found in executive functions, visuospatial skills, and social cognition domain.

Table 5. Cognitive differences between HD phenotypes

	Motor - (Behav | Cog | Behav + Cog) n = 13		**Motor + (Behav | Cog | Behav + Cog) n = 26**		**U**
	Md	**IRQ 25 –75**	**Md**	**IRQ 25 –75**	**p**
Executive z-compound	-0.3	-0.9 – -0.2	-1.2	-2.0 – -0.2	.068
Attention z-compound	-1.6	-2.5 – -0.3	-1.9	-3.1 – -0.6	.633
Visuospatial z-compound	-0.7	-1.8 – -0.4	-0.5	-2.3 – 0.1	.625
Memory z-compound	-2.3	-2.8 – -1.9	-2.3	-3.7 – -1.9	.357
Language z-compound	-2.1	-2.5 – -1.5	-1.5	-2.9 – -1.0	.323
Social cog. z-compound	-1.0	-1.5 – -0.3	-1.3	-2.6 – -0.6	.324

Note: Table 5 outlines the main differences in cognitive profile between the two primary phenotype groups: Motor -, and Motor +, focusing on six cognitive domains: executive functioning, attention, visuospatial skills, memory, language, and social cognition. Abbreviations: Md = median, IRQ = interquartile range, U = Mann-Whitney test, p = p-value.

Our investigation of symptom onset revealed notable differences in prevalence patterns (see Table 6). Particularly, among participants in the Motor - group, a combined presentation of behavioral and cognitive symptoms was the most common, accounting for 57.1% of cases. Simultaneously, this combination also outnumbered any other symptom combination in the Motor + group. The next most frequent phenotype encompassed the behavioral symptoms in the Motor - group (35.7%), closely followed by a combined motor and cognitive phenotype in the Motor + group (35.3%). Motor symptoms, either alone or in combination with behavioral, appeared in 17.6% of cases. Finally, the least prevalent phenotype among our participants was the cognitive phenotype (7.1%).

Table 6. Phenotype prevalence at onset

	Motor - (Behav | Cog | Behav + Cog) n = 13	**Motor + (Behav | Cog | Behav + Cog) n = 26**
Behav	35.7%	0.0%
Cog	7.1%	0.0%
Behav + Cog	57.1%	0.0%
Motor	0.0%	17.6%
Motor + Behav	0.0%	17.6%
Motor + Cog	0.0%	35.3%

Note: Table 6 provides an overview of the onset prevalence of two main phenotypes, Motor - and Motor +, as well as more specific phenotypes: behavioral, cognitive, behavioral + cognitive, motor, motor + behavioral, and motor + cognitive. Due to low percentage values, the percentage bars are capped at a maximum of 60%.

The median overall behavioral score was 6.0 ($IRQ_{25\text{-}75}$ = 0.0 – 10.3) for the Motor - group and 4.0 ($IRQ_{25\text{-}75}$ = 0.0 – 17.0) for the Motor + group, indicating no significant difference, p = .833 (see Table 4). In the similar manner, there we did not observe any statistically significant differences in specific behavioral symptoms between these groups (see Table 7). Overall, the most prevalent symptom in both groups was depression (Motor +: 58.0%; Motor -: 69.0%), closely followed by anxiety (Motor +: 46.0%; Motor -: 54.0%). In contrast, the least prevalent symptoms were delirium and hallucinations. The Motor – group showed slightly higher rates of depressive symptoms, low self-esteem/guilt, anxiety, suicidal ideations/thoughts, obsessions, and compulsions. On the contrary, the Motor + group exhibited moderately higher levels of aggressivity, irritability, delirium, and hallucination.

Table 7. Behavioral differences between HD phenotypes

	Motor - **(Behav | Cog | Behav + Cog)** **n = 13**	**Motor +** **(Behav | Cog | Behav + Cog)** **n = 26**	**FET**
	Percentage	**Percentage**	**p**
Depression	69.0%	58.0%	.728
Low self-esteem/Guilt	23.0%	15.0%	.666
Anxiety	54.0%	46.0%	.741
Suicidal ideations/thoughts	23.0%	7.0%	.310
Aggression	23.0%	35.0%	.714
Irritability	23.0%	39.0%	.477
Obsessions	8.0%	4.0%	.999
Compulsions	8.0%	0.0%	.333
Delirium	0.0%	4.0%	.999
Hallucinations	0.0%	4.0%	.999

Note: Table 7 displays prevalence of behavioral symptoms from the behavioral component of the UHDRS between the two HD phenotypes. Abbreviations: FET = Fisher's exact test, p = p-value.

4 DISCUSSIONS

In this work, we focused on examining differences across disease stages and phenotypic variations in patients with genetically confirmed HD, by comparing demographic, clinical, and neuroimaging data collected during comprehensive neurological, neuropsychological, and neuroradiological evaluations conducted at Padua University Hospital.

The primary aim was to investigate three HD stages: presymptomatic, prodromal, and manifest, based on the diagnostic criteria proposed by Reilmann et al. (2014). We found no significant demographic differences among these stages. Genetically, the median CAG repeat length across these stages ranged from 41 to 43, aligning with the typical adult onset in the mid-40s (Nopoulos, 2016).

No statistically significant differences were observed in structural changes in white matter (WM) and gray matter (GM) atrophy across the three stages. However, we observed a trend of decreasing T-scores with a more pronounced decline in WM compared to GM, though WM degeneration appears more severe. This trend aligns with findings in previous studies, which have noted that WM degeneration of precedes and/or exceeds GM loss in HD, which may reflect greater vulnerability of WM to demyelination and disrupted connectivity (Casella et al., 2020; Fennema-Nostine et al., 2004; Niccolini & Politis, 2014; Poudel et al., 2014).

A statistically significant difference emerged in the motor component of the UHDRS, indicating motor symptom progression with disease advancement (Oosterloo et al, 2021; Siesling et al., 1998; Stoker et al., 2022). Specfically, we found that the TMS, encompassing chorea and rigidity, effectively distinguish the manifest stage from both presymptomatic and prodromal stages, with no significant differences between the presymptomatic and prodromal stages (Franciosi et al., 2013; Siesling et al., 1998). Interestingly, chorea exhibited a significantly increasing trend across stages, which constrasts with previous findings (Jacobs et al., 2016; Siesling et al., 1998).

Furthermore, we observed a statistically significant functional decline over time on the functional scales of the UHDRS, including the Functional Assessment (FAS), the Total Functional Capacity (TFC), and the Independence Scale (IS) (Franciosi et al., 2013; Oosterloo et al., 2021; Siesling et al., 1998). Similar to the motor component of the UHDRS, the functional scales of the UHRDS effectively differentiated the manifest stage from the presymotomatic and prodromal stages (Franciosi et al., 2013). No significant

difference was found between the presymptomatic and prodromal stages, likely due to the delayed onset of functional imparment in HD (Tabrizi et al., 2022).

Cognitive functioning showed a statistically significant decline in both global cognition and specific cognitive domain. General cognitive decline was assessed using the MMSE and the MoCA, with scores decreasing as the disease progressed (Toh et al., 2014). The MMSE was sensitive in distinguishing between the prodromal and manifest stages, likely due to its discriminatory ability in the total score, as well as in domains such as memory, visuospatial abilities, and orientation (Mestre et al., 2018). In contrast, MoCA identified statistically significant differences even between the presymptomatic and manifest groups, suggesting the MoCA's heightened sensitivity in detecting cognitive changes across multiple domains, especially in visuospatial abilites, language, and memory. Additionally, the MoCA includes sensitive measures of executive functioning, a component that is less present in the MMSE (Mickes et al., 2010; Toh et al., 2014).

Specific cognitive domains (executive functions, attention, visuospatial skills, memory, language, and social cognition) demonstrated significant deterioration over time, particularly in the prodromal and manifest stages. Notably, the presymptomatic group displayed no signficant impairments in any of the aforementioned domains, indicating subtle cognitive decline at this stage (Duff et al., 2008; Toh et al., 2014).

Executive functioning significantly declined over time, with statistically significant differences between the presymptomatic and manifest stages and between the prodromal and manifest stage. However, considering the *z-score* treshold of -1.5 (where values below indicate pathology), no clinically significant pathology was present across the three stages, which may be associated with selective executive dysfunction, suggesting that some executive functions such as decision-making, may remain intact while others, for instance verbal fluency, may decline (Bachoud-Lévi et al., 2001; Holl et al., 2013; Larsen et al., 2015; Snowden et al., 2001).

The attention domain showed a significant linear trend, suggesting progressive attentional decline. Additionally, attention was useful in differentiating among all three stage comparisons: presymptomatic versus prodromal, presymptomatic versus manfiest, and prodromal versus manifest. The significant discrimination between the presymptomatic and prodromal groups reflects early attentional deficits resulting from subcortical abnormalities. Furthermore, attentional deficits commonly parallel executive dysfunction, which was not the case in our study, possibly reflecting different compensatory mechanisms within their underlying networks. Moreover, the clinical

significance of pathological performance reached in the manifest stage may lead to inability to perform certain tasks, compromising the functional independence (Craufurd & Snowden, 2002; Paulsen et al, 2013; Pini et al., 2020; Snowden et al., 2001).

We observed significant decline in visuospatial abilities, with significant differences between the presymptomatic and manifest stages, and between the prodromal and manifest stages, but not between the presymptomatic and prodromal stages. Similar to the executive domain, visuospatial impairments did not reach clinically pathological performance (*z-score* below -1.5) even in the manifest stage, suggesting a delayed onset. Although some studies have reported early visuospatial deficits, this contrast may be associated with selective dysfunction, as allocentric abilities tend to deteriorate in the early stages, while egocentric decline later in the diseases (Bachoud-Lévi et al., 2001; Mohr et al., 1991; Paulsen & Conybeare, 2005).

Memory was found to significantly deteriorate along with the disease progression. Statistically significant differences were observed in manifest group when compared to presymptomatic as well as prodromal group, which is consistent with previous findings. Furthermore, memory deficits exhibited clinically significant pathology in the prodromal stage. This acute onset may be attributed to the failure of compensatory mechanisms that are still active during the presymptomatic stage (Bachoud-Lévi et al., 2001; Harrington et al., 2012; Papoutsi et al., 2014; Snowden et al.,2001; Toh et al., 2014).

On the other hand, deficits in domains such as memory tend to have a more acute onset, occuring closer to the clinical course of the disease, with incremental progression (Montoya et al., 2006b).

Language abilities also worsened over time, with statistically significant differences observed between the manifest group and the presymptomatic and prodromal groups (Bachoud-Lévi et al., 2001; Gagnon et al., 2018). However, clinically significant decline was only evident in the manifest stage (Azambuja et al., 2012), likely related to high attentional demands (Craufurd & Snowden, 2002).

We found a statistically significant progression in social cognition deterioration across HD stages, with significant differences between the presymptomatic and prodromal groups, as well as between the presymptomatic and manifest groups. However, no clinically pathological performance was observed, which suggests subtle and gradual onset of these deficits. Additionally, the presymptomatic disturbances in social cognition domain correspond with previous findings, indicating that social cognition is one of the early affected functions (Bora et al., 2016; Turner et al., 2022). This typically arises with

heightened personal distress and primarily manifests as difficulities in recognizing negative emotions. Moreover, social cognition itself is a complex construct, encompassing several domains like empathy, Theory of Mind, alexithymia, and more. These components are underpinned by different mechanisms involving the limbic system, anterior insula, and prefrontal cortex, all of which begin to deteriorate early in HD (Mason et al., 2021; Petersén & Gabery, 2012; Wolf et al., 2007).

Behavioral abnormalities did not display statistically significant worsening across the HD stages, though their progression warrants discussion. First, depression tends to manifest early in the disease and worsen over time, alinging with literature that links it to fronto-temporal pathology (Mayberg, 2001). In contrast, other studies report an improvement in depressive symptoms over time (Paulsen et al., 2005), potentially due to treatment interventions and/or onset of apathy in later stages (Ramos & Garrett, 2017).

Low self-esteem and guilt appeared absent in the intial stages of HD, but increased with as the disease progressed, potentially due to overall functional decline and social stigmatization (Lechich, 2008). Anxiety was highly prevalent in the presymptomatic stage, with a noticable decrease over time, suggesting that anxiety symptoms may develop independently of HD neuropathology rather than as a direct consequence (Anderson & Marder, 2001; Dale & Duijn, 2015).

Suicidiality was also higher in the presymptomatic stage, consistent with previous research, suggesting that suicidal ideations may be related to receiving positive HD diagnosis, therefore, their prevalence increases the early stages of the disease. Additionally, suicidality has a comorbidity with other psychiatric manifestations, such as depression and anxiety, which also occur in the initial stages. This highlights the importance of clinically assessing these symptoms (Goh et al., 2018; Nopoulos, 2016; Paulsen et al., 2017). Aggression and irritability tended to worsen from the premanifest to prodromal stage but showed slight improvement in the manifest stage, possibly linked to apathy symptoms that tend to take over behavioral symptoms as the disease advances (Craufurd & Snowden, 2002; Ramos & Garrett, 2017).

Obsessive-compulsive symptoms primarily emerged in the prodromal stage but were relatively uncommon, which may be due to several factors. For instance, obsessions and compulsions share similar underlying mechanisms with executive functions (Anderson et al., 2010). Therefore, preserved executive functioning in the early stages, due to selective executive dysfunction, may correlate with the absence of obsessive and compulsive symptoms. Additonally, the absence of complex, valid, and reliable

measurement tools may contribute to this observation, as most clinical assessments include only a single item related to each symptom (Anderson et al., 2010; Paulsen et al., 2017).

Delirium and hallucinations were rare and appeared only in the manfiest stage. This may be linked to absence of genetic factors, as the development of psychotic symptoms in HD is often associated with familial predisposition, as well as their typically low prevalence in HD (Rosenblatt, 2007; Tsuang et al., 2020).

Our secondary aim was to examine the differences between HD phenotypes based on their initial symptoms, either with the presence (Motor +) or absence (Motor -) of motor manifestations. No significant differences were found in the demographic information between the two stages, although cognitive and/or behavioral onset without motor symptoms was more prevalent in female participants, whereas motor onset was more common in male participants (Zielonka et al., 2013). Age of onset was higher in the Motor + group, aligning with the previous research suggesting that behavioral and cognitive symptoms tend to precede motor abnormalities (Paulsen et al., 2017; Roth, 2019). No statistically significant differences were found in the CAG triplet expansion or structural changes (WM and GM atrophy) between the two groups.

Regarding motor symptoms, the Motor + group showed significantly higher TMS and chorea scores than the Motor - group. This may associated with the possible total absence of motor symptoms in some participants from the Motor - group. Additionally, these results may reflect the progressive nature of motor symptoms (Oosterloo et al, 2021; Siesling et al., 1998; Stoker et al., 2022).

In the terms of functional abilities, we observed lower functional independence in the Motor + group, with statistical significance only for the Functional Assessment subscale (FAS) of UHDRS. This suggests a greater impact of motor symptoms on the HD patient's functionality than neuropsychiatric symptoms (Gibson et al., 2021).

Notably, no statistically significant differences were found in the global cognition, or across specific domains, indicating that the presence of prevalent motor onset does not discriminate across cognitive performances. These results contrast with previous findings suggesting that poor cognitive performance is associated with the severity of motor symptoms (Duff et al., 2008). However, in the Motor + group, we still observed slightly higher executive and attentional dysfunction (Hart et al., 2014) and social cognition disruption (Cavallo et al., 2022).

Behavioral symptoms such as depression, low self-esteem/guilt, anxiety, sucidial ideations/thoughts, obsessions, and compulsion were more prevalent in the group without

initial motor symptoms. In contrast, aggression and irritability were more prevalent in the Motor + group (Duijn et al., 2013), as well as delusions and hallucinations which may be associated with the exacerbation of motor symptoms (Craufurd & Snowden, 2002). However, none of these comparisons were stastistically significant.

Finally, we explored phenotype prevalence at onset. We observed that the most common initial symptoms were behavioral, either alone or in combination with cognitive deficits, suggesting that these manifestations often precede motor alterations (Paulsen et al., 2017; Roth, 2019). Interestingly, the combination of motor and cognitive phenotypes was also relatively common, however, these results require further investigations.

The practical implications of this work include the potential implementation of our results into clinical practice for tracking disease progression. Primarily, cognitive and functional deficits, as well as motor deficits, were found to be useful in distinguishing between different HD stages. Notably, the attention and social cognition domains were the only ones that differentiated between the presymptomatic and prodromal stages. Furthermore, we offer a new perspective on the categorization of HD phenotypes based on the presence or absence of initial motor alteration. Although our preliminary investigation did not yield significant findings, given the complexity and heterogeneity of the disease (Kremer, 2002) it is becoming increasingly important to track and understand diverse clinical presentations, as they may lead to different disease progressions, emphasizing the relevance of precision medicine approach (Konig et al., 2017).

Like all studies, our thesis has limitations. One issue is the small sample size, as well as the small number of participants across the various groups. Another limitation is that not all of participants underwent the same neuropsychological assessment, due to severity of certain symptoms that prevented some participants from completing the evaluations. Another challenge is the behavioral assessment, mainly due to patients' loss of insight, which diminishes from the reliability of their answers, but also due to lack of valid tools and instruments that could be reported by caregivers (Mestre, 2016). Additionally, the determination of the presence of motor symptoms in the initial stages relied on the patient's clinical histories, and as the subtle cognitive and behavioral changes are often overlooked, this might affect the first reported symptom and, consequently, our categorization.

Based on our findings and limitations, we suggest that future research replicate our study with a larger number of participants in each group to improve generalizability. We also highlight the need for further investigations into the potenial differentiation between

presymptomatic and prodromal stages based on attentional decline and disruptions in social cognition. Finally, future research may incorporate functional neuroimaging assessment in addition to structural evaluations to explore potential functional discrepancies between the two HD phenotypes.

5 CONCLUSIONS

Within our thesis, we first explored the differences across three HD stages: presymptomatic, prodromal, and manifest. We observed statistically significant differences across all stage, particularly when comparing the manifest stage to the presymptomatic and prodromal stages. These results were significant for motor manifestations (TMS, rigidity, and chorea), functional decline (FAS, TCF, and IS), and cognitive deficits, both global (MMSE, MoCA), and domain specific (executive, attention, visuospatial, memory, language, and social cognition). These findings suggest a general worsening of symptom as the disease progresses. Attention and social cognition were statistically significant in distinguishing between the presymptomatic and prodromal stages, however, future research may investigate these results in greater depth. Furthermore, none of the participants from the presymptomatic group exhibited clinically significant pathology in their cognitive performance. The progression of behavioral symptoms across stages was not found to be significant, highlighting the need for further investigation. Developing more sensitive behavioral assessment tools, including those that can be administered to caregivers, could enhance our understanding of behavioral changes in HD and consequently improve diagnosis.

Secondly, we investigated specific HD phenotypes assigned according to the initial symptom presentation into two main groups: cognitive and/or behavioral phenotype without motor manifestations, and a motor phenotype with cognitive and/or behavioral abnormalities. The non-motor group showed significantly less impairment in motor functions (TMS and chorea) and greater functional independence (FAS) than the motor group. No statistically significant differences were observed in cognitive and behavioral profiles. Regarding phenotype prevalence at onset, the most prevalent were behavioral symptoms either alone or combined with cognitive deficits, close followed by a combination of motor and cognitive symptoms. Our resutls indicate that motor symptoms may have greater impact on functional capacity than neuropsychiatric symptoms. Finally, motor alterations do not appear to impact cognitive and behavioral performance, though future investigations on this topic are warranted. Further research is needed to examine HD phenotypes in greater depth, as they may display variability in disease progression. Notetheless, recognizing and understanding these differences is crucial, as they can guide the development of more tailored therapeutic and rehabilitative treatments.

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