Montreal cognitive assessment for evaluating cognitive impairment in Huntington's disease: a systematic review

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Abstract

Objective. This study aims to systematically review evidence of the accuracy of the Montreal Cognitive Assessment (MoCA) for evaluating the presence of cognitive impairment in patients with Huntington's disease (HD) and to outline the quality and quantity of research evidence available about the use of the MoCA in this population.

Methods. We conducted a systematic literature review, searching four databases from inception until April 2020.

Results. We identified 26 studies that met the inclusion criteria: two case–control studies comparing the MoCA to a battery of tests, three studies comparing MoCA to Mini-Mental State Examination, two studies estimating the prevalence of cognitive impairment in individuals with HD and 19 studies or clinical trials in which the MoCA was used as an instrument for the cognitive assessment of participants with HD. We found no cross-sectional studies in which participants received the index test (MoCA) and a reference standard diagnostic assessment composed of an extensive neuropsychological battery. The publication period ranged from 2010 to 2020.

Conclusions. In patients with HD, the MoCA provides information about disturbances in general cognitive function. Even if the MoCA demonstrated good sensitivity and specificity when used at the recommended threshold score of 26, further cross-sectional studies are required to examine the optimum cutoff score for detecting cognitive impairments in patients with HD. Moreover, more studies are necessary to determine whether the MoCA adequately assesses cognitive status in individuals with HD.

Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease caused by the expansion of CAG repeats in exon 1 of the huntingtin (HTT) gene at the short arm of chromosome 4 (4p16.9), responsible for the synthesis of the huntingtin protein. The disease was described in 1872 by Huntington.[1] Since the discovery of the gene locus near the tip of the short arm of chromosome 4 in 1983 and the cloning of the gene 10 years later, there has been an extensive research on the genetics of HD, although the exact role of the abnormal gene product HTT in neurodegeneration is still not well understood.

Genetic confirmation of CAG repeat expansion is the hallmark of current epidemiological measures of HD. Accurate prevalence estimates depend on comprehensive genetic testing coupled with neurological evaluation. Prevalence studies incorporating both genetic and clinical diagnostic standards show that 10.6 to 13.7 individuals per 100 000, are affected in Western populations.[2–5] Prevalence studies that include genetic (molecular) diagnostics report higher rates of the disease than those using clinical measures alone.[6] Longitudinal analyses show an increase in the prevalence of HD over the past several years, probably owing to the wider availability of the genetic testing.[3,7] The incidence of HD is estimated to be 4.7 to 6.9 new cases per million people per year in Western populations[8]; it is endemic to all populations but occurs at much higher frequencies among individuals of European ancestry. Populations in Japan, Taiwan, and Hong Kong have a much lower incidence of HD with a prevalence of one to seven cases per million people, approximately one-tenth as frequently as in Europe and North America.[5,9] In South Africa, black people also present with lower rates than white and mixed-ancestry subpopulations.[10,11] These differences are ancestry-specific,[4] relating to genetic differences in the HTT gene.

HD is diagnosed on the basis of clinical evaluation, family history, and, in most cases, genetic testing for the presence of the CAG expansion in HTT. The disease is a fully penetrant, autosomal-dominant, inherited disorder; therefore, a carrier of an expansion greater than 39 CAG repeats is genetically diagnosed with HD. The triad of symptoms that characterize

the condition are motor dysfunction (most typically chorea), cognitive impairment (eg, problems with executive functions, attention, and emotion recognition), and neuropsychiatric features (such as apathy and blunted affect).[6] The clinical diagnosis of manifest HD is based on the presence of motor manifestations, which are the best known and most visible symptoms in HD. Among them, involuntary movements are the most obvious. The motor findings are fairly sensitive and specific. However, patients with HD may exhibit a variety of movement disorders, with the most common being chorea, but also parkinsonism (characteristic of juvenile HD), ataxia, dystonia, bruxism, myoclonus, tics, and tourettism. Nonetheless, these signs appear chronologically late compared with other manifestations such as cognitive impairment.

Mild cognitive impairment (MCI) has been reported to be present in approximately 40% of people with premotor (or prodromal, genetically confirmed) HD.[12] At the onset of motor symptoms, MCI was found in 84% of patients with HD and dementia in 5% of patients with HD. After 5 years of motor symptoms, 24% of HD patients met the criteria for MCI and 69% met the criteria for dementia.[13]

Cognitive impairment begins prior to the clinical diagnosis of motor symptoms, in the premotor or premanifest period, and progresses gradually throughout the course of the disease.[14–16] The features of cognitive disability in HD are similar to disorders associated with subcortical brain pathology (eg, Parkinson's disease [PD]) but are dissimilar to Alzheimer disease.[17,18] HD differentially affects specific domains of cognition throughout the course of the disease. The impaired cognitive domains include executive function, mental flexibility, psychomotor performance, attention, working memory, and emotion recognition. The largest cross-sectional effect sizes between early manifest HD and controls were demonstrated in information processing speed, executive function, attention, memory, visuospatial skills, timing, and emotion processing.[15,16,19–21] These cognitive deficits are detectable in the premanifest stages and develop slowly. Among these cognitive deficits, motor planning/speed and sensory perceptual processing are cognitive domains that may be important for predicting progression in the premanifest population.[22] The earliest change and best predictor of disease progression is psychomotor slowing.[16,23–25] Executive difficulties in HD include problems in planning,[26,27] organization and sequencing,[23] cognitive flexibility, and set shifting.[26,28] A common practical difficulty observed in HD is in multitasking, with evidence of attention problems.[29]

Learning and retrieval of new information are affected, but the impairment differs from Alzheimer disease, with rapid forgetting being less pronounced.[17] Studies investigating memory in HD patients have shown proportionally poorer free recall than recognition memory and cued recall,[30–32] more passive learning strategies in HD than controls,[32] problems in source memory[33] and in prospective memory,[34] and relatively preserved retention from immediate to delayed recall. The profile of memory disturbances suggests a strong executive contribution to memory failures, in keeping with disrupted striatal–frontal pathways.[35] In addition to the problems in declarative memory (ie, explicit memory for material previously presented), people with HD show procedural memory impairments (ie, skill and habit learning).[36,37] Language (eg, syntax) impairments are demonstrated early in the disease course, with progressive difficulties evident in understanding and producing complex sentences. In addition, patients with HD commonly show reduced performance on verbal fluency tasks.[38,39]

A reduction in lexical capacity appears later and often might be overlooked.[40]

Disorientation, both in time and space, appears during the progression of HD, and the temporal orientation is altered earlier.[41–43] Visuospatial and visual perceptual impairments are present late in the course of the disease through interference with the integration and understanding of visual information.[41] Several studies reported that patients with HD have difficulties with high-level perceptual discrimination,[44,45] perceptual integration,[46] and constructional tasks,[47] which utilize executive processes. Spatially, people with HD present impairments on tasks involving mental rotation or manipulation of information[48,49] and a timed visual search.[50]

Some cognitive disturbances such as problems with initiation, lack of awareness of deficits, and disinhibition are at the intersection between cognitive and psychiatric domains.[12] Patients with HD can have social disengagement, decreased participation in conversation, and slowed mentation, often accompanied by lack of awareness of deficits and by impulsivity.[51]

The psychiatric and behavioral manifestations of the disease are also very debilitating. These include irritability, depression and suicidal ideation or attempts, anxiety, apathy, obsessions, paranoia, and hallucinations.

Other symptoms besides motor, cognitive, and psychiatric disorders are often present. Among those, weight loss, dysphagia, and sleep disturbance are sometimes the most prominent symptoms.[40] In addition, patients with HD might present other debilitating symptoms such as urinary incontinence, pain, excessive perspiration, hypersalivation, and reduced lung function and respiratory muscle strength.[40]

Although the clinical diagnosis of HD has traditionally been based on motor signs and symptoms, neuroimaging and other tests can support the diagnosis, primarily by ruling out other conditions. Typically, they are not necessary, especially if there is a characteristic presentation of an individual with a known family history and a positive genetic test. An MRI or computed tomography (CT) scan may reveal symmetrical striatal atrophy (and often, to a lesser degree, atrophy in other subcortical regions, cerebral cortical gray matter, and subcortical white matter). Such changes might be detectible even prior to the development of motor symptoms and are strongly suggestive of a diagnosis of HD.[6]

In HD, in contrast to other neurological disorders (eg, PD, MCI, HIV-associated neurocognitive disorders [HAND]), there is no "gold standard" definition for MCI and dementia.[52] Therefore, it is challenging to provide a formal definition of MCI or dementia in HD. Adopting the general neurological definition, MCI is delineated as the transition between normal cognition and dementia, in which an individual develops subjective cognitive symptoms with objective evidence of cognitive impairment on a standardized neuropsychological evaluation but is still functionally independent. When cognitive impairment progresses to affect daily functions, dementia is diagnosed. The diagnosis of HD dementia should include demonstrable evidence of impairment in at least two areas of cognition (eg, attention, information processing speed, executive functions, visuospatial abilities, memory) but without the requirement of memory impairment in the context of impaired functional abilities and a deteriorating course.[18] The adoption of these definitions carries the challenge of identifying functional impairment strictly associated with cognitive impairment in a complex disease such as HD, in which other clinical features may contribute to a functional limitation.[52]

However, applying an extensive battery of neuropsychological tests is time consuming, is expensive, necessitates trained personnel, and is generally not feasible in most facilities. Therefore, brief cognitive tests, such as the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE), could be useful in evaluating patients with HD. Recently, the International Parkinson and Movement Disorder Society (MDS) invited an international group of experts on cognition in HD to review and critique scales evaluating global cognitive performance in HD patients.[52] The authors retrieved all the manuscripts published before September 2016 and considered a total of 17 cognitive scales for in-depth assessment. None of the scales met the criteria for a "recommended" status. To assess the severity of cognitive dysfunction, the MoCA was "recommended with caveats." In addition, it was "suggested" as a screening tool for cognitive impairment. Eight scales were classified as "suggested" for the purpose of measuring cognitive dysfunction severity, namely the Unified Huntington's Disease Rating Scale (UHDRS) Cognitive Assessment, the cognitive section of the UHDRS-For Advanced Patients (FAP), the Alzheimer's Disease Assessment Scale—Cognitive Subscale, the Frontal Assessment Battery, the Mattis Dementia Rating Scale, the MMSE, and the Repeatable Battery for the Assessment of Neuropsychological Status.[52]

The MoCA was developed in 2005 for detecting MCI and has been shown to be highly sensitive and specific in the older adult population.[53] It is a brief bedside test; the administration time is approximately 10 minutes. The MoCA evaluates executive functions, memory, and attention, which are commonly affected in patients with HD, and also evaluates visuospatial functions, naming, language, abstraction, and orientation. Scores on the MoCA range from 0 to 30 points; a score of 25 or lower indicates cognitive dysfunction. This cutoff is now widely used as a threshold for detecting cognitive impairment and possible dementia. To minimize practice effects, three versions of the MoCA have been developed in English, which test the same domains, but the contents of the tasks are different. The alternative versions of the MoCA present comparable reliability to the original test.[54] Translations in multiple languages are also available.

Several studies have consistently reported that the MoCA has good overall psychometric properties and good sensitivity in identifying milder forms of cognitive impairment in many clinical conditions. Therefore, the MoCA has widespread international use and is recognized as one of the best screening tests for cognitive impairment.[55] For example, in MCI, the MoCA demonstrated excellent internal consistency, with a Cronbach's alpha of 0.83 on the standardized items.[53] The test–retest reliability was also good, with a mean change in MoCA scores from the first to second evaluation of 0.9 points.[53] In addition, in studies that applied Rasch analysis techniques, the researchers found that scores on the MoCA can be used to quantify the amount of cognitive ability a person has and can be used to track changes in cognitive functions over time.[56]

Validation studies of the MoCA have been conducted in patients with different types of neurological disorders, such as MCI,[57] Alzheimer's disease,[57] and PD.[58] Nonetheless, recent systematic reviews found that cutoff scores lower than 26 on the MoCA were likely to be more useful for optimal diagnostic accuracy in patients with stroke,[59] dementia (including Alzheimer's disease, vascular dementia, Lewy body dementia, and frontotemporal dementia),[60] MCI,[61] and HAND.[62]

Early diagnosis and specific care of cognitive impairment in individuals with HD are essential, as it is an important cause of functional disability and related outcomes. Although physicians tend to focus on motor disturbances, rather than cognitive impairments when considering treatment, probably because they are the most visible symptoms, several studies have demonstrated the impact of cognitive disturbances on patients and caretakers.[21] Cognitive impairment, along with motor disturbances and apathy, was demonstrated to be an independent predictor of disability.[63] In addition, cognitive disturbances determined a patient's quality of life,[63–66] while motor disturbances and depression were predictors of caregiver burden.[63]

There is currently no cure or treatment that can halt, slow, or reverse the progression of the disease. Based on the present knowledge, no pharmacological treatment is recommended for the treatment of cognitive symptoms. However, multiple rehabilitation strategies (speech therapy, occupational therapy, cognitive, and psychomotricity) might improve or stabilize transitorily cognitive functions at some point of time in the course of the disease.[40] Several clinical trials have investigated means to alleviate or reduce symptoms and slow progression in clinically diagnosed as well as prodromal HD, but most of the clinical trials used a total motor score and a measure of functional capacity as primary and secondary outcomes. However, recent research has suggested that traditional outcomes designed for diagnosed HD may lack sensitivity for individuals with early HD and those with prodromal HD; thus, cognitive, psychiatric, and new functional capacity outcomes should be assessed.[66,67] Therefore, the validation of new measures for cognition and psychiatric disturbances will be critical to efforts to better treat HD,[20] as neuropsychological assessment has a crucial role in the identification of cognitive changes in the early phases of the disease, in monitoring progression, and in the evaluations of therapeutic interventions outcomes.

The MoCA fulfils important feasibility criteria for use in clinical practice: it has a short administration time and with multiple translations. Furthermore, online training and certification are available on the MoCA website. The test has been proven to have good psychometric properties in other populations and to assess a broad range of cognitive domains. Therefore, the MoCA may help identify individuals with cognitive impairments that might require further assessments and specific care, facilitating access to appropriate services. Nonetheless, incorrectly evaluated as having cognitive impairment implies significant costs due to further unnecessary investigations. Furthermore, cognitive assessments have exceptional potential to determine excellent potential for the early detection of HD in persons with genetic risk and have exceptional potential to determine sensitive outcomes in clinical trials, where reliable cognitive tools are needed in order to detect changes secondary to interventions in HD.

To date, no assessment scale has been sufficiently investigated to be classified as "recommended" for evaluating cognitive impairment in individuals with HD.[52] Among the scales "suggested" by the MDS, there are two scales that were specifically designed for HD: the UHDRS Cognitive Assessment and the UHDRS-FAP cognitive section. However, data regarding their sensibility and specificity and test–retest reliability are lacking. In addition, the UHDRS Cognitive Assessment has only a reduced number of tests, and, therefore, it is not considered to be sufficient for evaluating all relevant cognitive domains in HD.[52] The UHDRS-FAP is "suggested" for assessing severity of cognitive impairment only in late stages of HD, and further research is needed regarding its ability to discriminate across stages of cognitive dysfunction.[52] The other scales "suggested" by the MDS were not developed specifically for HD. Among them, the MoCA is the only scale that is also "recommended with caveats" for assessing cognitive impairment in HD individuals.[52]

However, in the literature, there is conflicting evidence regarding the optimal cutoff of the MoCA score,[59–62] and the MDS reviewed the articles published before September 2016. Therefore, there is considerable value in determining the strength of the empirical evidence that supports the use of MoCA as a screening test for cognitive impairment in patients with HD.

We aim to collate evidence from different studies, integrating the existing information and providing data for rational decision-making, highlighting possible answers that are easily accessible to clinicians, health care providers, and policy makers. The objective of this systematic review is to evaluate research regarding the accuracy of the MoCA for diagnosing cognitive impairment in individuals with HD and to highlight the methodological quality (in terms of risk of bias) and quantity of evidence available in this regard. In addition, we aim to identify the gaps in the literature concerning this screening test.

Methods

The present systematic review was performed following the recommendations described in the Cochrane Handbook for Diagnostic Test Accuracy Reviews[68] and the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[69]

Search strategy and selection criteria

Figure 1 shows the search strategy used in the systematic review.

A computerized bibliographic search was performed from the inception of the database to April 2020 for the following databases:

Figure 1. Study selection flow chart.

MEDLINE/PubMed, Scopus, Latin American and Caribbean Health Sciences Literature (LILACS), and PsychINFO. In addition, a complementary manual search was performed on the MoCA website, and the reference lists of all relevant research papers were checked to identify possible additional studies.

The following key words were used: "Montreal Cognitive Assessment" or the acronym "MoCA" and "Huntington's disease" (MeSH). These search terms were used with PubMed database, the primary source of citations. Searches in other data sources used similar versions of these terms, appropriate for each database. We did not utilize search filters (the collection of terms aimed at reducing the number of results that needed to be screened) because our aim was to generate a comprehensive list of studies that would be suitable for answering the research question. Even the most sensitive filters have been found to miss relevant studies and perform inconsistently across subject areas and study designs, while at the same time, they have not significantly reduced the number of studies that need to be assessed for inclusion.[68,70] In addition, we did not apply any language restrictions to our search.

Two authors reviewed the title, abstract, and full text (when needed) of all retrieved research papers and assessed whether the study met the inclusion criteria. Disagreements were solved through discussion, and the participation of a third rater was not needed to address discrepancies.

To perform a systematic review of MoCA use in the context of HD, we selected all the studies in which the MoCA was used to assess the cognitive abilities in HD individuals. The main types of eligible studies, using the MoCA as an index test, were (i) cross-sectional studies in which participants received the index test (MoCA) and a reference standard diagnostic assessment; (ii) case–control studies comparing the MoCA to a battery of tests; (iii) studies comparing the MoCA to the MMSE, the most widely used screening instrument to detect cognitive impairment; (iv) studies estimating the prevalence of cognitive impairment in individuals with HD; and (v) studies or clinical trials in which the MoCA was used for the cognitive assessment of patients with HD.

We included studies reporting adults (over 18 years old) with confirmed HD in which the association between the MoCA score and cognitive impairment was assessed, with the MoCA being used as an index test. The index test was any full version of the MoCA. Although we expected to find the recommended cutoff score of 26 or below to differentiate normal cognition (scores of 26 and above) from impaired cognition (scores less than 26), we also included studies using other thresholds. The target condition was cognitive impairment, including MCI and dementia. As a reference standard for cognitive impairment, we used a complex neuropsychological assessment that evaluated at least five neurocognitive domains (including verbal and language, attention and working memory, abstraction, and executive function, learning and recall, speed of information processing, and motor skills), with consensual recommendations on appropriate tests. We excluded studies with fewer than 10 participants. In addition, we excluded studies with patients with confounding factors such as neurological disorders (eg, recent traumatic brain injury, CNS infections, stroke, other neurodegenerative disorders, and brain tumors), drug or alcohol addiction, and active infections.

In addition, the methodological quality of the studies was assessed by two authors independently, using the unmodified Quality Assessment of Diagnostic Accuracy Studies 2 tool.[68] Disagreements were solved through discussion.
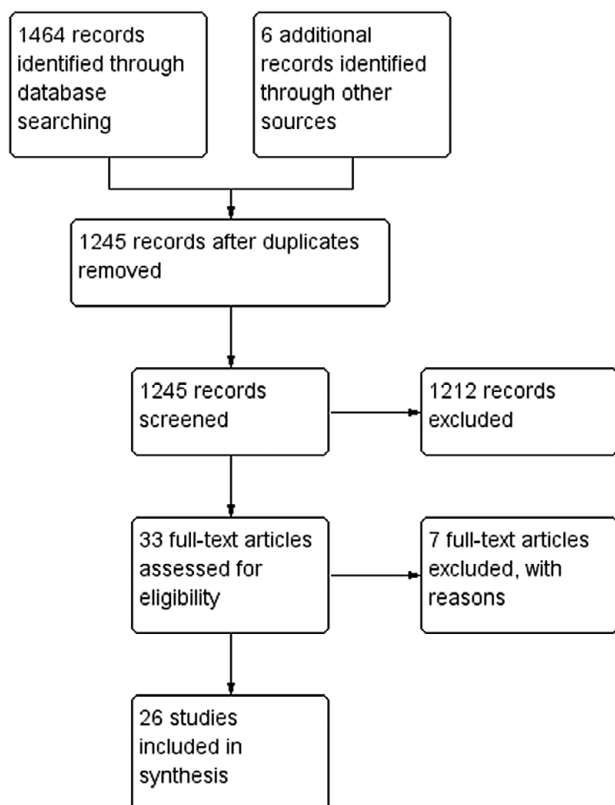
Results

From a total of 33 unique studies identified using the search strategy and assessed in the full-text, we included 26 studies in the present review: (i) two case–control studies comparing the MoCA to a battery of tests; (ii) three studies comparing the MoCA to the MMSE; (iii) two studies estimating the prevalence of cognitive impairment in individuals with HD; and (iv) 19 studies or clinical trials in which the MoCA was used for the cognitive assessment of participants with HD. We found no cross-sectional studies in which participants received the index test (MoCA) and a reference standard diagnostic assessment composed of an extensive neuropsychological battery.

The characteristics of the included studies are summarized in Table 1. The PRISMA diagram describing the selection process of studies is detailed in Figure 1.

Seven studies were excluded for the following reasons: the index test was not the MoCA (3), the study population consisted of less than 10 patients (3), or the research paper was in a language other than English or Spanish (1).

Twenty-six studies were included. The year of publication ranged from 2010 to 2020. The study samples were selected from 13 different countries (Australia, Brazil, Colombia, Czech Republic, France, Italy, Israel, Mexico, New Zeeland, Peru, Portugal, the UK, and the USA). Samples varied in size (10-109 participants), sex ratio (33.33%-72.22% females), median age (45-69.1 years), number of CAG repeats (42-46.05), MoCA scores, UHDRS motor scores, functional status, and educational level. The characteristics of the included studies are presented in Tables 1-3.

Case–control studies comparing the MoCA to a battery of tests (Tables 1 and 2)

To date, only two studies have assessed the validity of the MoCA as a screening tool for cognitive dysfunction in HD, using a cognitive battery as a reference standard.

The case–control study of Bezdicek and his colleagues[76] analyzed the results of the MoCA in correlation with a brief cognitive battery composite score. The neuropsychological functions of both the HD patients and the normal controls were assessed with the MoCA, and a short battery investigating five cognitive domains (memory, executive functions and set maintenance, set activation, psychomotor speed, and visuoconstructive functions).

The MoCA presented adequate internal consistency, with a Cronbach's alpha of 0.82 in HD patients. The concurrent validity of the MoCA total score and the composite score of the brief cognitive battery was $r = 0.81$ ($P < .001$) using the Spearman rank correlation coefficient. The HD patients scored significantly worse compared with normal controls on six of seven MoCA subtests, specifically the visuospatial/executive, attention, language, abstraction, delayed recall, and orientation subtests. HD patients were comparable to controls only in the naming subtest. The area under the curve (AUC; 95% CI) for the MoCA was 0.90 (0.809-0.997), and the optimal cutoff point was 25/26 (sensitivity = 0.94, specificity = 0.84, positive predictive value [PPV] = 0.81, negative predictive value [NPV] = 0.95) for all three measures; the point of maximum combined sensitivity and specificity, the optimal screening cutoff, and the optimal diagnostic cutoff.

The case–control study of Toh and his collaborators evaluated the utility of MoCA, MMSE, and UHDRS measures and a comprehensive neuropsychological battery of tests in monitoring short-term disease progression in HD patients.[78] The comprehensive assessment of cognitive function used 19 neuropsychological tests to assess six cognitive domains (executive function, working memory and attention, learning and memory, processing speed, language, and visuospatial functions). The number of tests administered was evenly distributed over two separate sessions that were 1 week apart; the tests were presented in the same order for all participants. Each session began with the MMSE in the first session and the MoCA in the second session. All returning participants were reassessed in an identical manner 12 months later. At baseline, 27.3% of the HD patients had normal cognition, 45.5% met the criteria for MCI, and 27.3% presented with dementia. All the controls had normal cognition. Compared to the controls, the HD group showed significantly reduced scores for overall global cognition and in brief cognitive tests both at baseline and at the 12-month follow-up.

In terms of domain-specific scores, the HD group had significantly lower scores than the controls across all cognitive domains and the mean effect sizes for baseline and 12-month follow-up combined ranged from the smallest ($d = 1.5$) in the language domain to the largest ($d = 2.8$) in the executive function domain. Relative to the control group, which showed an increase in the overall global cognitive z-score and the learning and memory domain score over a 12-month period, there was significantly less change in domain-specific scores in the HD group over that period. The MMSE and MoCA were less effective than the UHDRS cognitive assessment for monitoring cognitive changes in manifest HD patients over 12 months. The MoCA, MMSE, and UHDRS cognitive component scores correlated well with overall global cognition, as determined through the comprehensive neuropsychological test battery, in the HD group, supporting the utility of the three brief cognitive assessment tools in the cross-sectional detection of cognitive deficits in manifest HD patients. Furthermore, the results of the study indicated that there were no significant differences between the three brief cognitive tests reflecting overall global cognition in HD patients, thus providing no evidence that one test is better than the other in this respect. However, the UHDRS cognitive component, which focuses on testing executive function and had low variance over time, proved to be a more reliable brief substitute for comprehensive neuropsychological testing than the MMSE and MoCA in monitoring cognitive changes in HD patients after 12 months. With regard to the sensitivity and specificity of the MoCA, no data were presented.

From a methodological point of view,[68,97] both studies had a case–control design and were considered to present a high risk of bias, as there is consistent evidence that when using a case–control design in diagnostic accuracy studies, both sensitivity and specificity are increased.[68] In terms of the patients' spectrum risk of bias, the sensitivity of a test will often vary according to the severity of disease. The patient groups of both studies[76,78] were not composed of any presymptomatic HD subjects, and therefore, the conclusions cannot be generalized. In addition, the methods used to sample patients may lead to the inclusion of patients different from the spectrum in which the test will be used in practice; the ideal diagnostic accuracy study would prospectively include a consecutive series of patients fulfilling all selection criteria. In the aforementioned studies, it is unclear how the samples were recruited. Regarding the reference standard, the study of Bezdicek et al[76] used only a brief cognitive battery, and its incremental validity in relation to MoCA subscales is limited. Although Toh et al[78] used an extensive battery with 19 neuropsychological tests, this can also cause bias because the probability of an abnormal score increases as the number of tests performed per domain and the number of

Table 1. Characteristics of Included Studies

Study	Country of Origin	Study Type	Sample of HD	Gender (%)	Age (±SD)	Education (±SD)	No. of Nucleotide CAG Repeat (±SD)	Disease Duration (±SD)	MoCA (±SD)	MMSE (±SD)	Functional Status (±SD)	UHDRS Motor (±SD)
Mickes et al[71]	USA	Comparison to MMSE case–control	39	25 females (64.1%)	50.7±10.8	14.1±2.3	44.6±3.6 (range 40-57)	–	20.1±4.5 (range 11-29)	24.9±2.8 (range 19-30)	FCS 6.6±1.9	36.9±17.7 SD (range 10-76)
Videnovic et al[72]	USA	Comparison to MMSE	53	26 females (49.05%)	53±11.4	93% completed high school	–	8±5.9	21±4.4 (range 11-30)	26±2.4 (range 17-30)	TFC 7±3.4	33±16.7
Ferrara et al[73]	USA	MoCA used for cognitive assessment	11	4 females (36.36%)	54.5±13.7	13.6±4.7	43.1±2.5 (range 40-47)	–	19.4±5.4 (range 7-24)	–	TFC 6.5±3.3	29.8±10.5
Patel et al[74]	USA	MoCA used for cognitive assessment	11	6 females (54.54%)	47.6±4.7	–	44.4±1.3 (range 41-52)		24.6±1.1	–	–	27.2±5.6
Unschuld et al[75]	USA	MoCA used for cognitive assessment	12	6 females (50%)	46.3±7.9	16.3±3.2	43.8±2.8	7.7±3.1	25±4.7	28.4±1.9	–	–
Bezdicek et al[76]	Czech Republic	Case–control, comparison with a brief cognitive battery	20	8 females (40%)	49.6±13.3	13.5±2.6	42.7±6.9 (range 40-70)	–	20.5±5.5 (range 10-28)	–	FIS 86.0±15.3 (range 65-100)	25.1±9.5 (range 12-50)
Gluhm et al[77]	USA	Case–control; comparison to MMSE	104	58 females (55.8%)	49.9±11.5	14.1 (2.6)	44.7 (3.9)	–	19.3 (5.8)	23.7 (4.4)	TFC 7.3 (2.8) FIS 71.5 (13.6)	37.9 (17.7)
Toh et al[78]	New Zeeland	Case–control; MoCA and MMSE compared to a comprehensive neuropsychological (19 tests) assessing 6 cognitive domains	22	12 females (54.54%)	50 (15)	13 (2)	44 (4)	–	21.5 (4.9) (range 11-28)	26.5 (3.2) (range 19-30)		42.3±19.9 (range 11-82)
Cornejo-Olivas et al[79]	Peru	Observational descriptive—clinical and molecular characteristics	31	15 females (48.39%)	6.91±4.4 (range 60-77)	10.1	42.5±2.5	–	15.8±6.2 (range 7-26) available in 16 patients	22.8±4.2 (range 18-30) available in 15 patients)	–	–
Jacobs et al[80]	USA	MoCA used for cognitive assessment; case–control	18	13 females (72.22%)	45 (range 41-50)	–	43 (range 40-46)	–	23 (95% CI: 20-25)	–	DBS 344 (range 215-485)	13 (range 0-35)
Huntington Study Group[81]	Australia, USA	Randomized control trial MoCA used for cognitive assessment	109	55 females (50.46%)	51.9±11.0	–	43.9 (3.8)	–	23.0±3.9	–	FCS 9.2±2.1 FIS 81.6±12.2	32.6±16.2
Van Liew et al[82]	USA	Retrospective, case–control MoCA subtest used for assessment of memory	80	–	52.49±14.15	14.15±3.07	–	–	18.88±5.89	23.51±4.74	–	–
de Azevedo et al[83]	Brazil	MoCA used for cognitive assessment; case–control	26	14 females (53.85%)	49.42±10.83	–	42±3.79	–	22±2.12	–	–	21±4.24
Lagravinese et al[84]	Italy	MoCA used for cognitive assessment; case–control	15	7 females (46.66%)	53.6±9.6 (range 30-62)	11.86±3.6 (range 5-18)		8.1±5.7 (range 1-20)	19.87±5.68	–	TFC 10.9±2.15	36±19.5
Saba et al[85]	Brazil	MoCA used for cognitive assessment; case–control	11	6 females (54.54%)	45.7	–	44.2	5.6 (range 2-16)	15.2	21.2	–	39
Zitser et al[86]	Israel	Cross–sectional descriptive—clinical and demographic characteristics	84	–	–	–	–	–	–	–	–	–
Papoutsi et al[87]	UK	MoCA used for cognitive assessment	10	7 females (70%)	51.1±9.4	–	42.4±2.24	–	26.9±2.47	–	TFC 12.5±0.66	11.5±5.29

Table 1. *Continued*

Study	Country of Origin	Study Type	Sample of HD	Gender (%)	Age (±SD)	Education (±SD)	No. of Nucleotide CAG Repeat (±SD)	Disease Duration (±SD)	MoCA (±SD)	MMSE (±SD)	Functional Status (±SD)	UHDRS Motor (±SD)
Sousa et al[88]	Portugal	Cross-sectional MoCA used for cognitive assessment	29	17 females (58.6%)	50.03 ± 17.23	7.00 ± 3.36	−≥36	5.59 ± 5.78	15.73 ± 6.9 (apathetic HD) 24.93 ± 4.9 (nonapathetic HD)	–	–	36.93 ± 13.0 (apathetic HD) 14.14 ± 14.4 (nonapathetic HD)
Unti et al[89]	Italy	MoCA used for cognitive assessment; case–control	12	4 females (33.33%)	65.4 ± 10.3 (range 45-78)	8.6 ± 3.4 (range 5-13)	40.5 ± 2.5	–	18.5 ± 4.8	25.8 ± 2.2	–	36.6 ± 8.9
Atkinson-Clement et al[90]	France	MoCA used for cognitive assessment; case–control	15	11 females (73.33%)	57.8 ± 4.6	13.1 ± 3.6	–	9.3 ± 9.6	20.5 ± 5.9	–	–	–
Bayliss et al[91]	Mexico	MoCA used for cognitive assessment; case–control	12	8 females (67%)	42.7 (IQR 1.3)	16.0 (IQR 5.0)	–	–	24.5 ± 4.0	–	TFC 13.5 ± 1.2	12.5 (11.0)
Manor et al[92]	Israel	MoCA used for cognitive assessment; retrospective case series	14	–	48 ± 12	–	45.6 ± 4.3	4.2 ± 3.1	20.1 ± 4.1	–	–	36.7 ± 17.5
Purcell et al[93]	USA	MoCA used for cognitive assessment; case–control	17	7 females (41.18%)	55 ± 9.66 (range 36-67)	15.59 ± 2.67		5 ± 2.8 (range 3-13)	22.70 ± 3.46 (range 12-28)	–	ABC scale 81.20 ± 13.2 (range 50.31-100)	21.86 ± 9.86 (range 739)
Vaca-Palomares et al[94]	Mexico	MoCA used for cognitive assessment; case–control	22	13 females (59.09%)	49.6 ± 11.7 (range 29-68)	13.7 ± 3.0 (range 9-18)	44.3 ± 3.0 (range 40-52)	4.6 ± 3.0 (1-10)	24.2 ± 3.4	–	TFC 11.5 ± 2.1	17.0 ± 12.6
Valdés Hernández et al[95]	Colombia	MoCA used for cognitive assessment; case–control	15	8 females (53.33%)	45.87 ± 9.42	9.20 ± 3.19	–	–	17.07 ± 4.68	–	TFC 11.8 ± 1.5	–
Yitzhak et al[96]	Israel	MoCA used for cognitive assessment; case–control	21	9 females (45%)	47.38 ± 13.20	–	46.05 ± 5.70 (39-58)	–	20.71 ± 3.73 (15-26)	–	TFC 7.29 ± 2.80 (3-13)	37.55 ± 14.64 (12-73)

Abbreviations: ABC, activities-specific balance confidence; FCS, functional capacity score; HD, Huntington's disease; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; DBS, deep brain stimulation; FIS, Functional Independence Scal; IQR, interquartile range.

Table 2. Characteristics of Studies Using MoCA as an Instrument for the Cognitive Assessment of Participants with Huntington's disease

Study	Objectives	Methods	Results and Conclusions Considering MoCA
Ferrara et al[73]	To provide pilot data regarding tools that may be used to objectively assess the effects of tetrabenazine on hand function and balance. To evaluate three motor function tests, which might be useful in monitoring symptom progression and therapeutic response, pending formal validation.	The authors assessed 11 ambulatory patients with HD-related chorea on two occasions: (1) while off tetrabenazine (either prior to starting therapy or following a 24 h washout) and (2) when on a stable dose of tetrabenazine, titrated to optimal effect. Study evaluations included the JTHFT and Berg Balance Scale, a timed 25-foot walk, the MoCA, and the complete UHDRS.	• Performance on the JTHFT correlated with cognition, specifically the MoCA, but did not correlate with UHDRS maximal chorea scores. • The fact that motor performance on the JTHFT correlated with cognitive dysfunction but not chorea severity suggests that factors apart from chorea have a substantial impact on motor tasks. Pertinent impairments might include attention deficits and other deficiencies in executive function, as well as impairments in the ability to automatize behavior.
Patel et al[74]	To evaluate whether reflexive and voluntary orienting prove useful as biomarkers of disease severity in HD.	Eleven HD subjects were evaluated with the motor subscale of the UHDRS and the MoCA. Using an infrared eye tracker, the authors also measured latency and error rates of horizontal and vertical saccades using prosaccade and antisaccade eye movement tasks. They calculated simple and age-controlled correlations between eye movement and clinical parameters.	• The authors show for the first time that both reflexive and voluntary eye motor control in HD patients decrease with increase in disease severity suggesting declines in both motor and cognitive function.
Unschuld et al[75]	To identify the relationship of NAA and other brain metabolites to cognitive function in HD-mutation carriers by using high-field-strength MRS.	Individuals with the HD mutation in premanifest or early-stage disease and healthy controls underwent magnetic resonance spectroscopy (7.2 mL voxel in the posterior cingulate cortex) at 7 T, and also T1-weighted structural magnetic resonance imaging. All participants received standardized tests of cognitive functioning including the MoCA and MMSE and standardized quantified neurological examination within an hour before scanning.	• Linear regression with MoCA scores revealed significant correlations with NAA ($r^2 = 0.50$; $P = .01$) and glutamate ($r^2 = 0.64$, $P = .002$) in HD subjects. • There was no significant relationship measurable of NAA or glutamate with MMSE. A possible explanation could be that MoCA, unlike the MMSE, includes a subtest evaluating the executive functions. • The data suggest a relationship between reduced NAA and glutamate levels in the posterior cingulate cortex with cognitive decline in the early stages of HD. • NAA and glutamate magnetic resonance spectroscopy signals of the posterior cingulate cortex region may serve as potential biomarkers of disease progression or treatment outcome in HD and other neurodegenerative disorders with early cognitive dysfunction, when structural brain changes are still minor.
Jacobs et al[80]	To determine the domains of clinical balance impairments associated with HD; to evaluate associations between balance test scores and other disease-related impairments.	Subjects with genetically definite HD and age-matched control subjects were evaluated on the Mini-BESTest for their clinical balance impairments as well as the UHDRS motor and total functional capacity scales, ABC Scale-short form, MoCA, and SDMT.	• The Mini-BESTest scores significantly correlated with UHDRS motor and total functional capacity scores as well as with scores on the ABC short form, SDMT, and MoCA ($r^2 = 0.23$; $P = .046$) assessments.
Huntington Study Group[81]	To assess the safety, tolerability, and efficacy of PBT2, a metal protein-attenuating compound that might reduce metal-induced aggregation of mutant huntingtin in patients with HD.	Randomized, double-blind, placebo-controlled trial. The principal secondary endpoint was cognition, measured by the change from baseline to week 26 in the main composite z-score of five cognitive tests (Category Fluency Test, Trail Making Test Part B, Map Search, SDMT, and Stroop Word Reading Test) and scores on eight individual cognitive tests (the five aforementioned plus the Trail Making Test Part A, MoCA, and the Speeded Tapping Test).	• Compared with placebo, neither PBT2 100 mg nor PBT2 250 mg significantly improved the main composite cognition z-score between baseline and 26 wk. Compared with placebo, the Trail Making Test Part B score was improved between baseline and 26 wk in the PBT2 250 mg group, but not in the 100 mg group; neither dose significantly improved cognition on the other tests, including MoCA.
Van Liew et al[82]	To investigate whether the MoCA could provide a brief assessment of recall and recognition in AD and HD patients.	The retrospective, archival study included participants with HD, participants with AD, and community-dwelling control participants. Participants completed the MoCA as part of a more exhaustive cognitive and medical assessment, along	• The control participants performed significantly better than participants with AD at all the three levels of assessment.

Continued

Table 2. *Continued*

Study	Objectives	Methods	Results and Conclusions Considering MoCA
		with MMSE. Random effects hierarchical logistic regressions were performed to assess the relative performance of the normal control, participants with HD, and participants with AD on verbal free recall, cued recall, and multiple-choice recognition on the MoCA.	• No difference existed between participants with HD and controls for cued recall, but control participants performed significantly better than participants with HD on free recall and recognition. • The participants with HD performed significantly better than participants with AD at all the three levels of assessment. • The MoCA appears to be a valuable, brief cognitive assessment capable of identifying specific memory deficits consistent with known differences in memory profiles. • MoCA was capable not only of differentiating controls from participants with AD and HD at each level of memory performance (ie, free recall, cued recall, and multiple-choice recognition) but also of differentiating participants with AD and HD.
de Azevedo et al[83]	To perform a detailed evaluation of cerebellar morphology in HD patients.	HD patients and healthy controls were assessed with UHDRS and MoCA. The authors created a two-sample test to analyze cerebellar GM differences between groups and another to correlate GM alterations with UHDRS and MoCA, corrected for age, expanded cytosine-adenine-guanine repeats, and disease duration using the spatially unbiased atlas template (SUIT)-SPM-toolbox which preserves anatomical detailing.	• The study found increased GM density in the anterior cerebellum compared to controls. Higher GM density in the posterosuperior lobe correlated with mood symptoms. Worse motor function and better cognitive function correlated with GM changes in the posterior cerebellum. • Subjects with higher MoCA scores had higher GM density in lobule VIII on the left, which is involved in sensorimotor tasks and working memory, suggesting a cerebellar role in cognitive dysfunction in HD.
Lagravinese et al[84]	To assess whether the affective "ToM" ability is impaired in the mild to moderate stages of HD, and whether there is an association between compromised ToM ability and the presence of cognitive impairment.	ToM was evaluated by means of RMET and global cognitive functioning by means of the MoCA questionnaire in HD patients and healthy subjects.	• The study revealed that the ability to judge a person's mental states from a picture of their eyes was impaired in HD patients compared to normal population. • Neither in HD and healthy controls, a significant correlation emerged between MoCA total score and the percentage of correct responses at the RMET. • However, when the correlation was performed between the percentage of correct responses at the RMET and each of the six subscores of MoCA separately, RMET performance significantly correlated with the visuospatial abilities score but not with executive functions. • The results show that RMET might represent a valid instrument to assess affective ToM ability in HD patients in the mild to moderate stages of the disease, independently from their cognitive status.
Saba et al[85]	To evaluate the role of the involvement of white matter tracts in huntingtin gene mutation patients as a potential biomarker of the progression of the disease.	The authors performed brain magnetic resonance imaging to assess white matter integrity using DTI, with measurement of fractional anisotropy and evaluated participants with symptomatic huntingtin gene mutation, presymptomatic huntingtin gene mutation, and healthy controls. The participants underwent imaging studies and clinical evaluations, which included the UHDRS—motor part, MMSE, MoCA, and the Beck Depression Scale.	•The study data showed degeneration of many white matter tracts in patients with HD when compared to controls and presymptomatic individuals; however, the authors could not demonstrate differences between the presymptomatic and the control groups. • In conclusion, by using the DTI technique, HD patients exhibited extensively impaired white matter tracts, leading the authors to propose that changes in the diffusion parameters were associated with markers of the severity of the disease.

Table 2. *Continued*

Study	Objectives	Methods	Results and Conclusions Considering MoCA
Papoutsi et al[87]	To determine whether real-time fMRI neurofeedback training is feasible in HD and assess any factors that contribute to its effectiveness.	In this proof-of-concept study, the authors used a neurofeedback technique to train patients with HD to volitionally regulate the activity of their SMA. Detailed behavioral and neuroimaging data were collected before and after training to examine changes of brain function and structure and cognitive and motor performance. The participants were assessed with UHDRS—motor score and MoCA; selected cognitive and Q-Motor measures, independently validated as sensitive to disease progression in HD, were used to assess changes in cognitive and motor performance following neurofeedback training. The selected measures were combined into one composite score.	• The study presented preliminary evidence to suggest that neurofeedback training is feasible in HD and may induce disease relevant neuroplasticity with potentially beneficial effects on cognitive and motor function. • The composite score at the baseline visit correlated highly with the normalized CAG Age Product score, the MoCA, and UHDRS total motor score after controlling for age (all results were also significant without controlling for age). • The authors demonstrated that HD patients can learn to regulate their own brain activity using neurofeedback training. • The study identified the functional and structural changes that occurred during neurofeedback training, which correlated with cognitive and motor improvement in a set of (untrained) measures sensitive to disease progression. • Improved cognitive and motor performance after training predicted increases in pre-SMA GM volume, fMRI activity in the left putamen, and increased SMA–left putamen functional connectivity. • The data suggest that functional connectivity between the SMA and the left putamen may be a promising target for neurofeedback training. • In conclusion, the neurofeedback training can induce plasticity in patients with HD despite the presence of neurodegeneration, and the effects of training a single region may engage other regions and circuits implicated in disease pathology.
Sousa et al[88]	The aim of this study was to assess and compare apathy profile in PD and HD patients using the same comprehensive instruments to measure apathy, cognition, and depressive symptoms.	In all patients, information related to demographics, clinical data, motor score (Movement Disorders Society-Unified Parkinson Disease Rating Scale; UHDRS), cognition (MoCA), depressive symptoms (Beck Depression Inventory II), and apathy (Apathy Evaluation Scale—clinical version) was collected. Patients with dementia or major depression were excluded from the study.	• In HD patients, apathy was related to disease duration, motor score, and cognitive impairment. • Patients with PD and HD have similar prevalence of apathy but with different clinical correlations. • The cognitive profile of PD and HD apathetic patients is slightly different, with HD apathetic patients being significantly more impaired on attention, concentration and working memory, and language MoCA domains than PD apathetic patients. • Compared to nonapathetic HD patients, the cognitive profile of apathetic HD patients was significantly worse in short-term memory, executive, attention, concentration and working memory, language, and orientation domains of MoCA. • HD apathetic patients had a significantly higher duration of disease, significantly higher motor scores and more frequently presented with cognitive impairment than nonapathetic HD patients; in the correlation analysis, disease duration and cognitive impairment demonstrated a moderate positive correlation, whereas the motor score (UHDRS) demonstrated a strong positive correlation with apathy. • In the multivariate analysis, only motor score appeared to independently predict apathy.

Table 2. *Continued*

Study	Objectives	Methods	Results and Conclusions Considering MoCA
Unti et al[89]	To investigate the relationship between social cognition in HD patients and the plasma levels of the social hormone OT.	Mild-symptomatic HD patients (stage II Shoulson & Fahn) and matched healthy controls, without concurrent psychiatric disorders, were investigated at baseline (T0) for OT plasma levels and social cognition through an extensive battery of neuropsychological tests. Social cognition was also reexamined after 2 y (T1). A first battery of tests was used to investigate the cognitive abilities of the enrolled subjects: the MMSE, the MoCA, the FAB, and the Short-Term Intelligence Test. A second series of evaluations consisted instead of social cognition tests using the following questionnaires: the "Faux-Pas Task," the KDEF, the test of emotion attribution after a verbal trigger, the empathy "Strange Stories" test, and the Wilhelm Bush test.	• Results showed a trend for reduced T0-OT levels in HD compared to healthy controls but without reaching statistical significance. • At T0, patients showed significantly lower performances than controls at the "Faux-Pas" and "Strange Stories" tests; a reduced perception of visual emotions and verbal stimuli was also reported, involving anger, fear, and sadness. • The MoCA and MMSE scores positively correlated with psychosocial perception at the KDEF test; there was a positive correlation between MoCA scores at the baseline and Strange Stories, KDEF (in particular disgust), as well as MMSE at the baseline and Strange Stories, KDEF (in particular neutral). • The Wilcoxon analysis did not show any differences in MMSE and MoCA at T0 and T1.
Atkinson-Clement et al[90]	To confirm the relevance of using the DIP to quantify the psychosocial consequences of dysarthria in neurological diseases.	The case–control study evaluated patients with different kinds of dysarthria induced by several neurological disorders (PD, HD, dystonia, cerebellar ataxia, progressive supranuclear palsy—PSP, multiple system atrophy, lateral amyotrophic sclerosis). All participants underwent a cognitive evaluation (using MoCA) and a speech intelligibility assessment and completed three self-reported questionnaires: the 36-Item Short Form Health Survey, the VHI, and the DIP.	• The psychometric properties of the DIP were confirmed, including internal consistency ($\alpha = 0.93$), concurrent validity (correlation with the VHI: $r = -0.77$), and discriminant validity (accuracy = 0.93). • The absence of correlation between the DIP and the MoCA suggested that the DIP score is either not or only weakly driven by the cognitive status of the patients.
Bayliss et al[91]	To compare ToM task scores of patients with mild-to-moderate HD, their relatives (spouse or at-risk first-degree relative with a negative gene test) and unrelated healthy controls.	The cross-sectional study compared ToM scores of patients with mild-to-moderate HD, their relatives, and healthy controls; Individuals with dementia or depression were excluded; cognitive status was assessed with the Spanish version of the MoCA; the ToM test battery included Spanish versions of the RMET, Happé's Strange Stories (Social and Physical Stories subtests) and the Hinting Task.	• The Total Functional Capacity (TFC) scores correlated positively with the MoCA scores and negatively with the UHDRS. • The MoCA scores were not significantly different among groups, although 7/12 HD patients presented with mild cognitive impairment (MoCA score <26 points); the MoCA scores did not correlate with education across groups. • Across groups, cognitive ToM tasks and MoCA scores were positively correlated with Happé's Social Stories, Happé's Physical Stories, as well as the Hinting Task. • Cognitive ToM tasks scores were lower in HD patients than controls as well (Happé's Social Stories; the Hinting Task). • A previously reported correlation between RMET and MoCA scores in HD patients[84] was not replicated in this study.
Manor et al[92]	To characterize the swallowing disturbances of HD patients, to evaluate the feasibility of FEES in assessing dysphagia in HD patients, and to discern the relation between FEES findings and patients' self-report on dysphagia symptoms and SWAL-QOL.	The study retrospectively analyzed the data of HD patients that underwent BSE, FEES, the UHDRS, and the MoCA. All completed the SDQ and the SWAL-QOL questionnaire.	• HD patients exhibit prominent unique oropharyngeal dysphagia features that may serve as a marker of disease progression; the FEES and the SDQ are valuable tools for detecting these features in HD patients with swallowing disturbances. • The study found a negative correlation between the volitional cough and the cognitive test scores. • There was a significant positive correlation between the volitional cough and the ability to initiate volitional swallow; furthermore, the decrease in quality of the volitional cough also correlated negatively with the level of cognition.

Continued

Table 2. *Continued*

Study	Objectives	Methods	Results and Conclusions Considering MoCA
			• Swallowing therapy approaches and swallowing compensatory techniques should be adjusted to the patient's cognitive level; given that progressive decline in cognitive level is expected with HD progression, frequent visits to the speech and language pathologist may be indicated.
Purcell et al[93]	To determine the impact of DT interference, sensory feedback, and cognitive performance on balance and falls in HD.	Participants with HD and healthy controls underwent quantitative balance testing with APDM inertial sensors. Postural sway was assessed during conditions of manipulated stance, vision, proprioception, and cognitive demand. The DT was a concurrent verbal fluency task. The participants underwent were administered tests assessing multiple cognitive domains: Cognitive function was assessed with the following tests: MoCA (for global cognition), Digit Span forwards, backwards, and sequencing (WAIS-IV), SDMT, CERAD word list, JLO, and animal naming. The UHDRS motor section provided a total motor score (UHDRS TMS).	• HD participants presented worse postural control under DT, limited proprioception/vision, and greater DT interference with a narrowed base and no visual input. • HD participants scored significantly worse than controls on measures of global cognition (MoCA), response inhibition (Stroop), processing speed (SDMT), verbal fluency (COWAT), visuospatial abilities (JLO), and working memory (digit span). Unexpectedly, performance on memory delayed recall (CERAD word list) was not significantly different between HD participants and controls. • The authors did not find significant correlations between the domains of attention, executive function, memory, or global cognition and postural instability. • These findings may have implications for designing motor and cognitive strategies to improve balance in HD.
Vaca-Palomares et al[94]	To investigate the neural basis of the anticipatory behavioral deficits in HD.	The case–control study used a predictive-saccade paradigm that requires predictive control to generate saccades in a metronomic temporal pattern. The integrity of the oculomotor network that includes the striatum and prefrontal, parietal, occipital, and temporal cortices can be analyzed using structural MRI. The patient's evaluation included the MoCA to assess general cognitive functioning and to assess disease progression.	• HD patients presented severe predictive saccade deficits (ie, an inability to reduce saccade reaction time in predictive condition), which are accentuated in patients with more severe motor deterioration. • Structural imaging analyses revealed that these anticipatory deficits correlated with GM atrophy in frontal, parietal–occipital, and striatal regions. • These findings indicate that the predictive saccade control deficits in HD are related to an extended corticostriatal atrophy, suggesting that eye movement measurement could be a reliable marker of the progression of cognitive deficits in HD. • The results suggested that motor and cognitive abilities in HD do not decline equally together.
Valdés Hernández et al[95]	To evaluate, for the first time, whether PVS can be considered a neuroimaging marker that differentiates vulnerability vs overt HD, and their association with cognitive, functional, and behavioral indicators in HD patients and their first-degree relatives.	The study analyzed neuroimaging indicators of global atrophy, PVS burden, and GM tissue volume in the basal ganglia and thalami, in relation to behavioral, motor, and cognitive scores, in HD patients with overt disease manifestation and first-degree relatives not genetically tested, which represented a vulnerable group. Both groups were assessed using the UHDRS; in addition, HD patients were assessed with the Total Functional Capacity Scale (HDFCS). The cognitive status was assessed with the MoCA test, the IFS, and the Raven's Standard Progressive Matrices. A social cognition test indexing social emotion was performed by all study participants.	• Poor fluid intelligence as per the Raven's Standard Progressive Matrices was associated with global brain atrophy and PVS burden in HD patients; the GM volume in all subcortical structures, with the exception of the right globus pallidus, was associated with motor or cognitive scores. • Only the GM volume in the right putamen was associated with envy and MOCA scores in first-degree relatives. • The outcome from the IFS and MoCA tests correlated with the left/right caudate and right putaminal GM tissue volumes only in the patient group. • MoCA scores were associated with the right putaminal GM tissue volume in the family group. • In conclusion, striatal GM volume, global brain atrophy, and PVS burden may serve as differential indicators of disease manifestation in HD; the Raven's Standard Progressive Matrices could be a cognitive test worth to consider in the differentiation of vulnerability vs overt disease in HD.

Continued

Table 2. *Continued*

Study	Objectives	Methods	Results and Conclusions Considering MoCA
Yitzhak et al[96]	To examine emotion recognition in HD patients, using a novel approach to emotion recognition testing, assuming that real-life emotional cues are dynamic and often also subtle and nonstereotypical. To characterize emotion recognition in HD patients and controls. To examine how different factors, such as cognitive status, motor symptoms, depression symptoms, and an estimation of HD pathology progression, are correlated with emotion recognition decline in HD patients. To compare two possible predictors of emotion recognition performance: general cognitive screening and severity of motor symptom.	The HD patients were assessed with with the total functional capacity (TFC) scale and the motor section of UHDRS. Cognitive decline was evaluated with the MoCA. The participants also were assessed with the BDI-II and performed an Emotion Recognition Task. The study had a two (group) × 2 (stimulus set) × 6 (emotion) mixed design.	• The HD patients demonstrated poor emotion recognition; the deficit was predicted only by the severity of their motor symptoms, not by their cognitive status. • Emotion recognition rate was not uniquely predicted by any other examined factor; this lack of predictive power was true also for the cognitive screening, as measured by the MoCA. • As patients' motor symptoms were more prominent, their emotion recognition was poorer.

Abbreviations: ABC, activities-specific balance confidence; AD, Alzheimer's disease; BDI-II, Beck Depression Inventory-II; BSE, bed side swallowing evaluation; CERAD, consortium to establish a registry for Alzheimer's disease; DIP, dysarthria impact profile; DT, dual task; DTI, diffusion tensor imaging; FAB, frontal assessment battery; FCS, functional capacity score; FEES, fiberoptic endoscopic evaluation of swallowing; GM, gray matter; HD, Huntington's disease; IFS, INECO frontal screening; JLO, judgment of line orientation; JTHFT, Jebsen-Taylor Hand Function Test; KDEF, Karolinska Directed Emotional Faces; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; OT, oxytocin; PD, Parkinson's disease; PVS, perivascular spaces; RMET, reading mind in the eyes test; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SMA, supplementary motor area; SDMT, Symbol Digit Modalities Test; SDQ, swallowing disturbances questionnaire; SWAL-QOL, swallowing related quality of life; ToM, theory of mind; TMS, total motor score; UHDRS, Unified Huntington's Disease Rating Scale; VHI, Voice Handicap Index, APDM, APDM*; WAIS-IV, Wechsler Adult Intelligence Scale.

assessed domains increase.[98–100] Furthermore, in both studies,[76,78] it is unclear if the interpretation of the index test was done without knowledge of the results of the reference standard and vice versa (known as test review bias and diagnostic review bias, respectively) or if any patient withdrawals occurred. Empirical evidence shows that a lack of blinding procedures may increase sensitivity, but no systematic effect on specificity was noted.[97] Additionally, incomplete reporting of any withdrawals from the study that might have occurred hinders the evaluation of this aspect.[68]

Studies comparing the MoCA to the MMSE (Tables 1-3)

We identified only three studies that directly compared the MoCA with the MMSE, the latter being used as a reference standard.[71,72,77] One study had a cross-sectional design,[72] and the others were case–control studies.[71,77] A detailed presentation of the studies is provided in Table 3.

In terms of risk of bias, only one study specified that a consecutive sample of HD patients was recruited.[72] In addition, none of the studies specified whether the reference standard results were interpreted without knowledge of the results of the index test and vice versa or if there were any patients who dropped out from the study. Furthermore, using the MMSE as a reference standard introduced incorporation bias, as both tests have some similar items (eg, serial sevens, time, and orientation). Incorporation of the index test in the reference standard is likely to increase the amount of agreement between the results, thereby leading to an overestimation of diagnostic accuracy.[68]

Studies estimating the prevalence of cognitive impairment in individuals with HD (Tables 1 and 2)

We identified two studies that used the MoCA to assess the prevalence of cognitive impairment in an HD population.[79,86] Both studies were descriptive, presenting clinical and demographic characteristics of HD patients.

Studies or clinical trials in which the MoCA was used as an instrument for the cognitive assessment of participants with HD (Tables 1 and 2)

The MoCA was used in 19 studies as a cognitive assessment scale. Only two clinical trials used the MoCA to evaluate the cognitive status of the HD individuals.[73,81]

The scale was used in six neuroimaging studies,[75,83,85,87,94,95] eight cognitive studies,[74,82,84,88,89,91,93,96] and three studies examining other clinical aspects of HD (eg, balance, dysphagia).[80,90,92]

Discussion

The present systematic review allowed us to make several key observations.

To date, research on the use of the MoCA in individuals with HD is somewhat limited. There is no high-quality cross-sectional study to assess the accuracy of the MoCA in screening cognitive impairment in this population. Only one case–control study compared the MoCA to a short cognitive battery.[76] The research provided very useful information, demonstrating that the test has robust psychometric properties: good concurrent validity, high sensitivity and high specificity in the detection of cognitive dysfunction in HD patients, and adequate internal consistency.

Table 3. Characteristics of Studies Comparing MoCA to MMSE

Study	Objective	Methods	Results	Limitations
Mickes et al[71]	To explore whether the MoCA would be more sensitive to mild to moderate cognitive impairment in HD than the MMSE.	The study used the ROC analysis to examine performance of HD and control groups on both tests on overall scores and scores from various subdomains.	• The HD group scored significantly lower than the control group on the MoCA and MMSE total scores. • Within-group comparisons indicated that both the HD and control groups had lower total scores on the MoCA relative to the MMSE. • The AUC values demonstrate that both tests significantly discriminated HD from CC subjects on total scores. • The MoCA score yielded higher sensitivity while maintaining a comparable level of specificity relative to the MMSE. • A similar pattern was found in the memory domain, with both tests accomplishing successful group discrimination; MoCA, however, yielded higher sensitivity and comparable specificity. • Only the MoCA, and not the MMSE, yielded significant AUC values for visuospatial and language scores, with higher sensitivity and specificity relative to the comparable MMSE domains. • The MMSE showed superior discrimination on orientation. • The MoCA executive function/attention score yielded a significant AUC for group discrimination.	• Relatively low sample of patients. • Selection of subjects with HD focused on those with mild to moderate symptoms represents a potential limitation for the generalizability of these findings to more severely impaired subjects. • Without additional neuropsychological testing, it is difficult to estimate appropriate cutoffs for patient groups.
Videnovic et al[72]	To compare the MoCA with the MMSE as a screening tool for cognitive dysfunction among patients with HD.	• The study recruited a consecutive sample of HD sample. • MMSE and MoCA were administered on the same day in alternating order. • Cutoff scores of <26 (for MoCA) and <24 (for MMSE) were used as values indicative of cognitive impairment. • Associations of MoCA and MMSE scores with disease severity, UHDRS, and TFC were evaluated via Spearman rank correlations, with a significance level of P <.05.	• The mean score was 26 ± 2.4 for MMSE and 21 ± 4.4 for MoCA. • The MMSE score correlated with TFC. • The MoCA score correlated with TFC and motor UHDRS. • The range of scores on the MMSE was 17 to 30 and on the MoCA 11 to 30; the ceiling effect was mild, and maximal scores on the MMSE and MoCA were obtained in one participant. • Twenty-seven patients (51%) scored <26 on the MMSE, and 48 patients (91%) scored <26 on the MoCA. • The MMSE scores were <24 in 12 patients (23%), and MoCA scores were <24 in 43 patients (81%). • Twenty-one patients (81%) of those who scored ≥26 on the MMSE had the MoCA score <26. • Thirty-two patients (78%) of those who scored ≥24 on the MMSE had the MoCA score <24. • None of the subjects who scored >24 or >26 on the MoCA had MMSE scores <24 or <26, respectively.	• The study cohort is relatively small. • The authors did not conduct a neuropsychological testing that is a gold standard for the assessment of cognitive performance. • Only cutoff scores of 24 and 26 were used as indicators of cognitive impairment.
Gluhm et al[77]	To examine the usefulness of MoCA for assessing cognitive performance in mild, moderate, and severe HD, compared with the use of the MMSE.	The authors compared MoCA and MMSE total scores and the number of correct answers in five cognitive-specific domains in manifest HD patients and matched controls. The MoCA and MMSE were administered on	• For the total HD sample and for the moderate and severe HD groups compared with normal controls, there were significant differences between both MoCA and MMSE total scores and all five cognitive-specific domains,	• The study used a convenience sample of HD patients from one academic center; however, this was a relatively well characterized group of patients.

Continued

Table 3. *Continued*

Study	Objective	Methods	Results	Limitations
		the same day in counterbalanced order.	except for language on the MMSE in moderate HD patients after Bonferroni correction. • Significant differences on the MoCA and MMSE emerged even for mild HD groups compared with normal controls with regard to total score and three (attention/executive function, memory, and orientation) of the five cognitive-specific domains after Bonferroni correction. • The MMSE showed significant differences on the visuospatial domain in mild HD patients compared with normal controls. • The effect sizes for differences between normal controls and each of the HD groups on MoCA and, to a slightly lesser degree, on MMSE were large for total scores and most cognitive-specific domains. • Mild HD patients did show significant impairment on the visuospatial domain of the MMSE compared with the MoCA. • MoCA was able to detect cognitive impairment across a wide range of severity in HD, suggesting it is a use full screening measure of cognitive performance in a nonselected HD population, although not necessarily superior to the more widely used MMSE.	• The study did not consider the effects of mood, medication, or concomitant disease on cognitive testing. • Normal controls had no reported history of neurological or psychiatric disorders and no use of psychoactive substances or medications; however, the authors did not use additional standardized assessments of functional or psychiatric performance to exclude subjects.

Abbreviations: AUC, area under the curve; HD, Huntington's disease; ROC, receiver operating characteristic; MoCA, Montreal cognitive assessment; MMSE, mini-mental state examination; TFC, total functional capacity; UHDRS, unified Huntington's disease rating scale.

Interestingly, the optimal screening and diagnostic cutoff was a score of 26, which is concordant with the original study on the MoCA.[53] However, this information must be interpreted with caution, as the authors used only a brief cognitive battery, and its incremental validity in relation to MoCA subscales is limited. Although this is one of the most informative studies conducted in this domain, it presents certain limitations (eg, the sample of patients was relatively low, and the study group was not composed of any presymptomatic HD subjects).

The second case–control study that investigated the utility of the MoCA in HD samples, compared it to a comprehensive neuropsychological battery, composed of 19 neuropsychological tests to assess six domains of cognitive function.[78] Although the study did not provide any information on the sensitivity and specificity of the MoCA in the HD population, it provided a new perspective on the utility of two widely used brief cognitive assessment tools (the MMSE and MoCA) in comparison to the UHDRS cognitive assessment and other measures for monitoring cognitive changes in manifest HD patients over a 12-month period. The authors concluded that the MMSE and MoCA are less useful for monitoring longitudinal cognitive changes over short-time intervals and the UHDRS cognitive assessment, which focuses on testing executive function, is more sensitive to short-term cognitive changes, and is a more reliable brief assessment tool than the MMSE and

MoCA over a period of 12 months.[78] Nonetheless, we must interpret these results with caution.

In the present study, the criteria for MCI followed that described for PD by Dalrymple-Alford et al,[101] with a requirement of two measures at—1.5 SD or equivalent within a single domain; the raw score of each component test in the neuropsychological battery was converted to a standard *z*-score using test-specific norms so that objective comparison could be made across component tests, regardless of individual scale ranges and distributions.[78] Studies have demonstrated that, assuming a normal distribution of test scores, 7% of people scoring 1.5 SD or more below the mean would be falsely designated as having cognitive decline, even without any change in performance over time (ie, false-positives). The requirement for impaired performance on at least two tests reduces the risk for false-positives but not false-negatives. In PD patients, for example, one study found that the best criterion to minimize the inclusion of cognitively normal patients as having MCI was to require deficits of at least—1.5 SD in two scores within any single domain (resulting in 30% MCI) or deficits of at least—1.5 SD in two scores from different domains (37% PD-MCI).[101] Furthermore, studies of complex neuropsychological batteries in healthy controls report that between 15% and 22% of individuals from a normal control group and 20% of a simulated normal population will score below the threshold for cognitive impairment, with false-positive

results.[100] These errors are caused by two common practices to increase sensitivity regarding milder neurocognitive abnormalities. First, extensive test batteries will have higher false-positive rates than individual tests because they involve multiple comparisons. The probability of an abnormal score increases as the number of tests performed per domain and the number of assessed domains increase (ie, diagnosing a normal individual as impaired). Second, the high cutoff scores (z-scores with a threshold of 1 SD) will increase the overlap between critical portions of test score distributions in individuals with and without disease.[98,100] The result of increased sensitivity is essentially a reduction in specificity. Therefore, false-positive cases will lead to biased prevalence estimates and reductions in power for analytical estimates.[100,102]

The MoCA was also compared with the MMSE, the most widely used screening instrument for cognitive impairment. The MMSE was used as a reference standard in three studies[71,72,77] with somewhat contradictory results. The study of Mickes and his colleagues,[71] using receiver operating characteristic (ROC) analysis, reported that almost all five cognitive-specific domains on the MoCA, but only two on the MMSE, significantly differentiated a sample of mild to moderate HD patients from normal controls. In contrast, a later study[77] found that significant differences between both MoCA and MMSE total scores and almost all cognitive-specific domains emerged. Even mild HD subjects showed significant differences with regard to total score and several cognitive domains on both instruments. The authors concluded that the MoCA is a useful instrument for assessing cognitive performance over a broad level of functioning in HD but is not necessarily superior to the MMSE.[77] One possible reason for this discrepancy is the difference in the sample size used in the studies; furthermore, the study of Mickes and his colleagues[71] excluded serial sevens from analysis. Finally, another study involving moderately impaired HD patients with a mean UHDRS total functional capacity (TFC) score of 7.0 concluded that the MoCA, compared with the MMSE, may be a more sensitive screening instrument for cognitive dysfunction in HD patients on the basis of cutoff points.[72] The different results of the latter study might be due to a different study design: the study of Videnovic and his colleagues[72] was cross-sectional and the other two studies[71,77] had a case–control design. The case–control studies are usually considered to present a high risk of bias, compared to cross-sectional studies, as there is consistent evidence that in diagnostic accuracy studies, when using a case–control design, both sensitivity and specificity are increased.[68] Nonetheless, we must keep in mind that, for other neurological disorders, the MoCA also presented superior sensitivity for detecting MCI compared with the MMSE, as the MoCA contains more demanding tasks for assessing executive and memory functions.[103]

When comparing the MoCA directly to the MMSE, all three studies that were conducted involving HD patients presented an incorporation bias, as both tests contain some similar items (eg, serial sevens, time, and orientation). This is likely to increase the amount of agreement between index test results and the reference standard and to overestimate the diagnostic accuracy of the MoCA.[68] Finally, there is evidence that the administration of both tests in one session leads to a high level of interference, specifically between the MoCA delayed recall subtest and the MMSE three-word recall subtest, as well as between repeated trials of serial sevens.[104]

The MoCA has also been used as a tool of cognitive assessment in various studies with HD individuals. However, although the scale is "suggested" by the MDS for the screening of the presence of cognitive dysfunction in HD patients and "recommended with caveats" for assessing the severity of cognitive dysfunction,[52] the results of the MoCA must be interpreted with caution. The data regarding the use of the MoCA in HD patients are quite limited, and the use of this brief cognitive assessment tool requires additional comprehensive testing for complete validation to determine the severity of cognitive dysfunction.[52]

Nonetheless, the studies that used the MoCA as a cognitive assessment tool in participants with HD provided some important information. The MoCA scores correlated with motor function tests, suggesting that factors apart from chorea have an impact on motor tasks (eg, executive functions).[73] In addition, reflexive and voluntary eye motor control,[74] balance,[80] and volitional cough[92] were correlated with cognitive function as revealed by the MoCA. On the other hand, no correlation was found with the dysarthria scores[90] and postural instability.[93] This may be because cognitive and motor abilities do not decline equally together.[94]

Furthermore, the MoCA proved to be a valuable tool that is capable of differentiating participants with AD and HD and able to identify specific memory deficits.[82] The MoCA scores also presented a positive correlation with the TFC scores[91] and a moderate correlation with apathy.[88] With regards to the "theory of mind" or the ability to attribute mental states (to oneself and others), which was found to be impaired in patients with HD, Reading Mind in the Eyes Test performance was correlated with visuospatial abilities as assessed by the MoCA in one study,[84] but these findings were not replicated by later research.[91] Some studies, investigating social cognition in HD, found that the MoCA scores were correlated with tasks of social cognition tests,[89] but others reported that emotion recognition was not predicted by the MoCA.[96]

Neuroimaging studies revealed that MoCA scores present significant correlation with N-acetylaspartate (NAA) and glutamate brain levels[75] and with gray matter density in the cerebellum[83] and subcortical structures.[95]

To date, the MoCA has rarely been used as a cognitive assessment tool in clinical trials. In a study investigating the safety, tolerability, and efficacy of a metal protein-attenuating compound that might reduce metal-induced aggregation of mutant HTT, although the scores on the Trial Making test part B were improved after treatment, though the MoCA scores did not show significant improvement.[81] However, another study, intended to provide pilot data regarding tools that may be used to objectively assess the effects of tetrabenazine on hand function and balance, showed that the performance on the Jebsen-Taylor Hand Function Test (JTHFT) correlated with cognition, specifically the MoCA, but did not correlate with UHDRS maximal chorea scores.[73] In addition, in a neurofeedback training study, MoCA scores revealed improvement in cognition.[87]

Although the MoCA seems to be a promising screening test for people with HD, our systematic review found that further studies are necessary regarding this issue. Even if the MoCA demonstrated good sensitivity and specificity when used at the recommended threshold score of 26, studies conducted in patients with different types of neurological disorders revealed that lowering the threshold offers a better balance between true-positive and false-positive results.[59–62] Therefore, the MoCA deserves closer scrutiny to assess its properties in the HD population. Further studies are necessary to determine whether the MoCA adequately assesses cognitive status in HD individuals. In addition, further cross-sectional studies are required to examine the optimum cutoff score for detecting cognitive impairments in patients with HD.

The present review confirms the main potential benefit of the MoCA as a test promising to significantly decrease the cognitive assessment time and costs, with robust psychometric properties—

good concurrent validity and adequate internal consistency. However, the optimal threshold should probably be further investigated. In addition, different thresholds should be tested in individuals with multiple cultural and educational backgrounds and speaking different languages. Researchers should also consider the value of the MoCA in a diagnostic workup so that clinicians can understand how to use this screening test to attain relevant outcomes for patients, such as the benefits of earlier diagnosis. Nonetheless, patients with abnormal screening results should be further assessed with a full neuropsychological assessment. A stepwise protocol including cognitive screening would be easy to implement in routine clinical practice and would show physicians how to address this complex problem.

After publication of the MDS recommendations regarding the cognitive rating scales to be used in HD individuals, the number of research papers reporting the use of MoCA in HD increased. Before 2017, MoCA was used in one prevalence study,[79] one neuroimaging study,[75] two cognitive studies,[74,82] two clinical trials,[73,81] and one study regarding clinical aspects of HD.[80] In addition, all the diagnostic test accuracy studies[71,72,76–78] were published before 2017. In the last 4 years, 14 studies reported the use of MoCA in HD patients: one prevalence study,[86] five neuroimaging studies,[83,85,87,94,95] six cognitive studies,[84,88,89,91,93,96] and two studies investigating clinical aspects of HD.[90,92] Nonetheless, the last diagnostic test accuracy study was done in 2013.[77]

Our systematic review identified several research gaps regarding the use of the MoCA in HD individuals. The most important gap is the need to conduct high-quality, cross-sectional studies in order to obtain data regarding the optimal threshold for detecting cognitive impairment in this population. Moreover, there is a need to investigate the use of the MoCA in different HD stages, including the prodromal stage. Another consideration for future research is the fact that more longitudinal studies are needed to investigate whether MoCA can be a reliable instrument for assessing changes in cognitive function over time. Besides, future clinical trials should use both, the MoCA and an extensive neuropsychological battery, to document whether the MoCA correctly identifies cognitive changes after treatment.

Our study has certain limitations as we did not perform any meta-analyses because the extensive literature search revealed only a low number of studies, with relatively small samples of patients. Also, the included studies had significant heterogeneity among them with regard to study design, patient samples, demographic differences, language and educational background, and reference standard. In any case, the presentation of the studies investigating the use of the MoCA in HD patients provided both an overall picture of the current state of the evidence in the field and identified knowledge gaps in the matter. The results of the present synthesis allowed us to illustrate several research gaps, including the absence of studies, and the lack of knowledge around optimal cutoff, delineating areas of future research initiatives. In addition, the results of quality appraisal were summarized to offer a general impression of the validity of the available evidence.

In conclusion, despite the limitations mentioned before, our study represents the first systematic review of the literature published in this field and describes an accurate state of knowledge on the use of the MoCA in people with HD.

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