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Huntington study group's neuropsychology working group position on best practice recommendations for the clinical neuropsychological evaluation of patients with Huntington disease

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ABSTRACT

Objective: Neuropsychological evaluation is critical to detection and management of cognitive and neuropsychiatric changes associated with Huntington disease (HD). Accurate assessment of non-motor complications of HD is critical given the prominent impact on functional disability, frequently commensurate with or exceeding that of motor symptoms. The increasing emphasis on developing disease-modifying therapies targeting cognitive decline in HD requires consensus on clinical neuropsychological assessment methods. The Neuropsychology Working Group (NPWG) of the Huntington Study Group (HSG) sought to provide evidence and consensus-based, practical guidelines for the evaluation of cognitive and neuropsychiatric symptoms associated with HD. **Method**: The NPWG recruited a multi-disciplinary group of neuropsychologists, neurologists, and psychiatrists to inform best practices in assessing, diagnosing, and treating the non-motor symptoms in HD. A review was circulated among the NPWG, and in an iterative process informed by reviewed literature, best practices in neuropsychological evaluation of patients with HD were identified. **Results**: A brief review of the available literature and rational for a clinical consensus battery is offered. **Conclusion**: Clinical neuropsychologists are uniquely positioned to both detect and characterize the non-motor symptoms in HD, and further,

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provide neurologists and allied health professions with clinically meaningful information that impacts functional outcomes and quality of life. The NPWG provides guidance on best practices to clinical neuropsychologists in this statement. A companion paper operationalizing clinical application of previous research-based non-motor diagnostic criteria for HD is forthcoming, which also advises on non-motor symptom screening methods for the non-neuropsychologist working with HD.

Introduction

Huntington Disease (HD) is a neurodegenerative disease characterized by progressive cognitive, psychiatric, and motor dysfunction. Current diagnostic criteria rely on motor signs, such that a clinician has 99% confidence that extrapyramidal motor signs are due to HD in a patient with a family history of HD or genetically confirmed gene expansion carrier. However, research supports the presence of both cognitive and behavioral/psychiatric phenotypes that may emerge a decade or more before motor signs and have been associated with functional declines (Hamilton et al., 2003; Hendel et al., 2022). Indeed, up to 65% of patients with HD have at least one psychiatric or cognitive symptom at time of motor diagnosis (McAllister et al., 2021). Further, it is not uncommon for individuals with cognitive and psychiatric symptoms to be diagnosed with mental health disorders rather than HD (e.g. early psychiatric symptoms diagnosed as bipolar disorder), especially in late onset HD, which may mislead clinical intervention, prognosis, and functional planning (Chaganti et al., 2017). To consider non-motor signs in the diagnosis of HD, the Movement Disorder Society (MDS) commissioned a Task Force to discuss and produce a set of recommendations (Ross et al., 2019). Briefly, the Task Force recommended incorporating objective signs of cognitive decline and the nosology of the Diagnostic and Statistical Manual, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) to allow for a cognitive-predominant manifest HD diagnosis; psychiatric symptoms were deemed insufficiently specific to HD to represent an independent diagnostic option for manifest of HD. The proposal has not been without opposition, with McAllister et al. (2021) arguing that subjective cognitive *symptoms* (ie, patient-reported concern) is similarly non-specific to HD pathology as psychiatric symptoms and therefore neither should be used in diagnosing manifest HD disease (McAllister et al., 2021).

In the setting of the MDS Task Force opinion and concerns by others about subjective cognitive symptoms being non-specific, neuropsychologists are a natural specialty to lead the development, evaluation, and refinement of a proposed clinical diagnostic framework for non-motor manifestations of HD. The neuropsychological evaluation goes beyond symptom report, using objective and statistically validated metrics to inform differential diagnosis, improve sensitivity in monitoring of clinical status, and guide multidisciplinary treatment plan for patients with neurobehavioral disorders. Presently, there is a lack of uniform approach in the clinical neuropsychological practice of patients with a family history of HD. Therefore, the objective of this paper is to provide consensus best practice recommendations related to the

clinical neuropsychological evaluation of HD that can facilitate early detection and tracking of non-motor symptoms of HD within the framework proposed by the MDS Task Force.

Materials and methods

The Huntington Study Group (HSG) re-established a dormant Neuropsychology Working Group (NPWG) in 2019 (Co-Chairs: CMC, MAR). The NPWG recruited a multi-disciplinary group of neuropsychologists, neurologists, and psychiatrists with significant experience in HD to discuss these objectives over 6 months in 2021. This position paper summarizes the opinion of the NPWG regarding best clinical neuropsychological practice guidelines for the HD patient population. An informal consensus approach among the group members and an unstructured literature review was used to form this opinion. The HSG's Research Advisory Council (RAC) reviewed the opinion and comments were considered and integrated. A companion position paper by the same group outlines the consensus opinion of the NPWG regarding the implementation of non-motor diagnostic criteria in patients with HD, which is more broadly oriented to the entire clinical practice community (Figure 1, Ross et al. 2019).

Proposed protocol for neuropsychological evaluation of non-motor manifestations of Huntington disease

Introduction

NPWG formally recommends that a neuropsychological evaluation be considered an essential component for clinical diagnosis of a suspected cognitive-phenotype HD manifest diagnosis, with the understanding that full evaluations are not always feasible

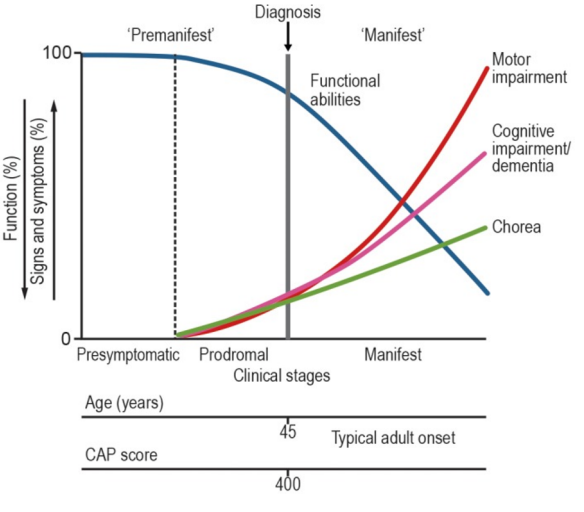

Figure 1. Clinical stages of Huntington disease.
Note. Image is used under open-source agreement of the associated publication, with acknowledgement to Ross et al. (2019).

and may be cost-prohibitive. A full neuropsychological evaluation affords greater sensitivity than cognitive screening measures (e.g. MOCA, MMSE), which may not detect cognitive impairment on their own (Roebuck-Spencer et al., 2017). Neuropsychological evaluation can identify or exclude confounding/alternative etiologies including polypharmacy, sleep apnea, and substance use disorder. Furthermore, neuropsychological evaluation can often delineate multiple contributions to cognitive-functional decline in HD, such as adjustment-reactive stress, interference from motor signs, behavioral/psychiatric factors, or early dementing processes not related to HD. Lastly, early cognitive detection and clinical diagnosis is important for all stakeholders in multidisciplinary care, which is the preferred model of care in HD, and assists in treatment planning across multiple disciplines, including neurology, neuropsychiatry, mental health practitioners, physical therapy, and speech therapy. Additional benefits include early intervention, eligibility for clinical research, and establishing cognitive baselines that may impact patients subsequently (e.g. applications for disability benefits or other accommodations).

The following recommendations aim to advance a field-wide consensus on the "gold standard" of neuropsychological evaluation for HD patients, while also offering practical guidance to providers with less experience or breadth of resources who may encounter the occasional HD referral in the community. The recommendations are intended to be adaptable depending on the setting (e.g. multi-disciplinary visit vs. regular outpatient neuropsychological services), available resources, demographic characteristics of the local community, and referral question.

Part 1: clinical history

As with any neuropsychological evaluation, delineating the onset and course of signs and symptoms (motor and non-motor in the case of HD) is of utmost importance. Motor signs are progressive but sometimes ameliorated by medication. Cognitive symptoms are progressive and infrequently responsive to medications and may fluctuate depending on environmental demands (e.g. perceived cognitive improvement following a shift to a less demanding job) (Mo et al., 2015) or other confounding factors (e.g. sleep disturbance, substance use, polypharmacy, or comorbid medical conditions) (Barker et al., 2020; Gibson et al., 2021; Saavedra et al., 2018; Tanigaki et al., 2020). Behavioral/psychiatric symptoms frequently fluctuate and are sometimes modified by medication.

The nature of the clinical interview differs by setting. Outside of a multidisciplinary clinic, in which patients may be concurrently assessed by a psychiatrist or neuropsychiatrist, a thorough psychiatric history and review of current emotional functioning is imperative. Collateral report, both *via* clinical interview and informant questionnaires, is also essential due to the high incidence of anosognosia in patients with HD (Isaacs et al., 2020; Wibawa et al., 2020). Detailed review of the patient's functional status is important for diagnosing neurocognitive disorders, staging, and for delineating motor versus non-motor interference.

A detailed family medical history should include questions about behavioral and motor signs in relatives who are at-risk of HD. Similarly, family history of other

neurological or movement disorders is important in that older family members may commonly have been misdiagnosed with more prevalent conditions such as Parkinson disease. When interviewing family members, clinicians should follow up on reports of a person as "acting odd," or having "the shakes," which may signal that they are observing elements of HD. Furthermore, substance abuse, arrests, temper outbursts, and suicide all may represent covert manifestations of HD.

As part of the neuropsychological evaluation in an HD referral, clinical interview should be used to build a lifelong picture of the features related to HD. The childhood history should include review for neurodevelopmental disorder diagnoses (e.g. ADHD, oppositional defiant disorder, or autism spectrum disorder). These conditions have elevated base rates incidence in HD CAG expansion carriers in childhood (Barkhuizen et al., 2018), probably due to multi-factorial etiology (subtle behavioral manifestation of HD, parenting style, risk of trauma/unstable environment, etc.). Even in the absence of neurodevelopmental disorders, psychological/physical neglect, abuse, and trauma exposure in childhood are common among this population (Forrest Keenan et al., 2007; Kjoelaas et al., 2022). Finally, antisocial personality traits (e.g. criminal activity) and adolescent substance use conditions are quite common (Byars et al., 2012; McDonell et al., 2021). Importantly, none of these conditions can be unequivocally attributed to early evidence of HD pathology, however, they contribute to the overall picture and enrich clinical understanding of the HD presentation.

Part 2: neuropsychological test battery

Rationale for consensus battery

Several neurocognitive disorders have benefitted from research aimed at defining standardized, brief, and reliable neuropsychological batteries, including Alzheimer's disease (CERAD) (Moms et al., 1989), multiple sclerosis (MACFIMS) (Benedict et al., 2002), and schizophrenia (MATRICS) (Green & Nuechterlein, 2004). Early intervention can delay onset, slow progression, and/or reduce disease severity in Alzheimer's disease (Norton et al., 2014; Rasmussen & Langerman, 2019), schizophrenia (Sommer et al., 2016), and multiple sclerosis (Cerqueira et al., 2018; Sumowski, 2015), which could be paramount in improving the quality of life for patients and their caregivers.

Relatively little is known about the implications of early detection and intervention on clinical outcomes in HD. As stated by Paulsen (2010), much "can be learned from our colleagues who have developed collaborative batteries for other brain disorders," like the CERAD, MATRICS, and MACFIMS (p. 7) (Paulsen, 2010). Paulsen outlined several steps that must be taken before a standardized cognitive battery for HD can be proposed, including (1) meticulous evaluation of the psychometric properties of the proposed measures, (2) identification of measures most sensitive to change in pre-manifest HD, (3) demonstration of feasibility for use in clinical trials and (4) minimization of redundancy in test measures by collaboratively building on the extant literature base. HD researchers have made strides in developing batteries for the investigation of cognition in clinical trials since Paulsen's call to action 10 years ago (Martinez-Horta et al., 2020; Stout et al., 2014). Yet, there remains a dearth of literature on validated, standardized neuropsychological batteries to assess neurocognitive progression in HD within

clinical contexts. This may be due, in part, to the domination of motor signs in the research landscape in clinical care and early intervention in HD (Paulsen, 2010). To achieve greater specificity in our understanding of the cognitive phenotypes in HD, we as a research and clinical community must move past viewing HD as primarily a movement disorder (i.e. diagnosing HD at motor symptom onset vs cognitive symptom onset), much the same as our colleagues moved beyond viewing schizophrenia as simply a psychiatric disorder. One step toward this goal is to collaboratively develop a standardized, consensus-driven neuropsychological battery for the assessment of cognition across the disease spectrum in HD, for use in both clinical and research settings.

Clinical application of research HD-CAB battery

The HD-Cognitive Assessment Battery (HD-CAB) represents a step forward and is a framework that can be augmented when developing an HD-specific neuropsychological test battery for clinical and research purposes (Stout et al., 2014). This brief (30 min) standardized battery, designed for use in clinical trial research, is comprised of six tests (Hopkins Verbal Learning Test—Revised, Symbol Digit Modalities Test, Trail Making Test Part B, Emotion Recognition, Paced Tapping, and One Touch Stocking). Administration of the full battery yields a composite z-score, which is sensitive in pre-HD and early HD group and shows high test-retest reliability ($r = 0.95$) (Stout et al., 2014). Several clinical trials and other research studies have utilized subtests of the HD-CAB (Baake et al., 2017; Fritz et al., 2016; Quinn et al., 2016; Reilmann et al., 2019; Schobel et al., 2017; Wasser et al., 2020). Recent efforts by members of this working group (Rossetti et al., 2023) aimed to adapt an HD-CAB informed battery for use in clinical settings, with several important findings. First, and perhaps most significantly, this work revealed the need for inclusion of additional measures to adequately assess all cognitive domains affected early in the HD-disease process (e.g. visuospatial processing) (Labuschagne et al., 2016; Lawrence et al., 2000). This is particularly relevant when evaluating an individual not yet formally diagnosed with HD, insofar as it allows for a gestalt impression and fosters an appropriately non-biased a priori approach for full differential diagnostic consideration. Second, alternate tests or forms were sometimes necessary due to factors unique to the clinical situation (e.g. measures with norms better suited to the population being seen, tests with superior clinical utility but perhaps less empirical support). Third, analyses demonstrated significantly different impairment rates in the executive functions domain depending on whether a timed versus untimed element was included in the paradigm. This warranted delineation and coverage of both timed and untimed approaches within the domain of executive functions. Finally, there was a need to include appropriate behavioral/psychiatric symptom inventories (self and collateral report), an issue not addressed in the HD-CAB paper. Thus, empirically informed best practice ideals must be balanced with feasibility and practical limitations inherent in the clinical setting. As such, we identified necessary domains of interest rather than specific cognitive tests or measures.

Clinical decision making in Test selection

Although the general nature and manner of assessment is somewhat consistent across neuropsychological settings and providers, the relative content and procedures vary

considerably depending on the goals of the evaluation, the specific questions being addressed (e.g. diagnostic clarification, functional capacity, rehabilitation and/or treatment planning), and the constraints/opportunities within the specific healthcare setting. In the case of a suspected cognitive-phenotype of HD, cognitive domains warranting specific attention include executive functions, processing/psychomotor speed, motor functions, attention/working memory, visuospatial and visual-object processing, as well as episodic and spatial memory (Glikmann-Johnston et al., 2019; Paulsen et al., 2017; Snowden et al., 2002; Solomon et al., 2007; Stout et al., 2012, 2014, Stout et al., 2011; Tabrizi et al., 2013). Moreover, the evaluation might include additional domains not routinely evaluated in neuropsychological practice. Although difficult to measure with standardized tests, procedural memory should be inquired about with patients with HD as they often forget previously well-learned skills such as playing an instrument, skiing, or riding a bike given the neuroanatomical substrate of the disease process (Paulsen, 2011). Additionally, social cognition, time perception, and decision-making are increasingly recognized as areas of impairment in HD, with important functional implications (Bora et al., 2016; Campbell et al., 2004; Kordsachia et al., 2017; Larsen et al., 2016; Mason et al., 2021; Stout et al., 2001; Vez et al., 2018). Relatedly, the recognition of affect, particularly for negative emotions, reflects an early cognitive change associated with HD (Henley et al., 2012; Johnson et al., 2007; Snowden et al., 2008). In addition to affective and decision-making aspects of HD, as with other movement disorders, the likely impact of motor function on some cognitive tasks must be considered and evaluated. As an example, the measurement of visual memory that requires the examinee to draw may be confounded by motor slowing or incoordination. Measures with minimal motor demands (e.g. recognition rather than reproduction of visual stimuli on a memory test) may be preferable, measures involving any graphomotor or oral-motor output may be affected by chorea and dysarthria. Due to the preponderance of anosognosia in HD, self-report forms as well as collateral questionnaires of mood and neurobehavioral symptoms are important adjuncts in a comprehensive assessment of patients with HD (Hergert et al., 2015; Hoth et al., 2007; Isaacs et al., 2020; Sitek et al., 2014).

NPWG proposed cognitive assessment

The NPWG has proposed a hierarchy of priorities for cognitive assessment (Table 1), that provides our Recommended (high priority, include whenever possible) or Encouraged (relevant, include when feasible and indicated) areas of cognitive testing, along with exemplars and alternative measures to use when evaluating patients at various levels of severity across the spectrum of HD. We recognize that measures sensitive to practice effect (ie, memory) should ideally have alternate forms or sufficient psychometrics in the literature to calculate reliable change estimates, though these may be more important in presymptomatic to prodromal range patients, rather than those with marked cognitive deficits. Rationales for test selection vary depending on clinic setting, and we do not propose a rigid approach or a fixed battery (note: full list of references for Table 1 is provided in Supplemental). Rather, we present guidelines aimed at ensuring a complete assessment of relevant cognitive and neurobehavioral domains.

An additional important aspect of any neuropsychological evaluation not addressed in Table 1 is the inclusion of performance validity testing (PVT). Per recent guidelines from the American Academy of Clinical Neuropsychology (Chafetz et al., 2015; Sweet, 2021) and a National Academy of Neuropsychology position paper (Bush et al., 2005), standalone and embedded measures are recommended for all neuropsychological evaluations. We identified one study that investigated PVT performance in people with HD (Sieck et al., 2013). The Test of Memory Malingering (TOMM), a forced-choice, visual recognition test, and an embedded PVT (Effort Index) on the Repeatable Battery for Neuropsychological Status (RBANS) were sensitive to detecting suboptimal engagement or poor effort in patients with HD (Sieck et al., 2013). Furthermore, they found that most HD patients passed both validity indicators, a finding consistent with prior research in various medical populations (Maiman et al., 2019). Those who failed either the TOMM or the RBANS Effort Index had both greater cognitive impairment and

Table 1. Neuropsychological Test battery for the clinical assessment in Huntington disease.

Assessment Method	Domain of Functioning	Inclusion Advice	Exemplars	Alternatives and Additions
Performance	Global Cognitive	Encouraged	• MoCA • PD-CRS	• MMSE
	Premorbid Intellectual	Recommended	• TOPF	• WRAT-4 Reading
	Attention & Processing Speed	Recommended	• TMT-A • WAIS-4 – Digit Span Forward • SDMT – written + oral • Stroop – word + color	• CPT-3 • DKEFS – Trails forms 1-3
	Visuoperception & Visuoconstruction	Encouraged	• RCFT Copy • RBANS Line Orientation	• HVOT
	Language	Recommended	• NAB – Naming • Animal Fluency	• DKEFS-Category Fluency • BNT
	Auditory-Verbal Memory	Recommended	• HVLT-R	• RAVLT • CVLT-3 • WMS-4-AMI • NAB Memory module subtests
	Visuospatial Memory	Encouraged	• BVMT-R	• RCFT • WMS-4-VMI • NAB Spatial Memory
	Executive (cognitive-control)	Recommended	• TMT-B • Stroop – Color/Word • COWAT/FAS • WAIS-4 – Digit Span Backwards	• DKEFS – Trails form 4 • DKEFS – Letter Fluency • DKEFS – C/WT
	Executive (problem-solving)	Encouraged	• DKEFS – Towers (achievement score) • WCST	• WAIS-4 – Similarities • WAIS-4 – Matrix Reasoning
	Socio-emotional	Encouraged	• ACS – Affect Recognition	• ACS other social perception subtests • Cambridge Emotion Recognition Task
	Motor	Recommended	• Grooved Pegboard	• Finger Tapping Test
	Sensory	Encouraged	• BSIT	• Sniffin' Sticks

(*Continued*)

Table 1. Continued.

Self & Informant Report	Depression / Suicide Risk	Recommended	• PHQ-9 • (note suicide item #9)	• PROMIS - Depression • BDI-2
	Anxiety	Recommended	• GAD-7	• PROMIS – Anxiety • BAI
	Sleep-wake	Encouraged	• ESS • PSQI	• PROMIS – Sleep Disturbance • PROMIS – Sleepiness-related Impairment
	Frontal-Behavioral Syndrome	Encouraged	• FrSBE (informant) • FrSBE (patient)	• b-DAS (informant)
	Anosognosia	Encouraged	• Anosognosia Scale	• FrSBE (patient v. informant)
	Neuropsychiatric Symptoms	Recommended	• PBA-s • NPI-Q (informant)	• BIS-11 • BVC
	Functional Status	Recommended	• HD-CFRS	• FAQ • WHODAS 2.0

Notes. Strength of advice: Recommended (high priority, include whenever possible) or Encouraged (relevant, include when feasible and indicated).

Tests in order of appearance (references in Supplemental).

MoCA: Montreal Cognitive Assessment; MMSE-2: PD-CRS: Parkinson Disease – Cognitive Rating Scale; Mini Mental Status Exam, Second Edition; Kokmen STMS: Kokmen Short Test of Mental Status; SLUMS: Saint Louis University Mental Status Examination; WRAT5: Wide Range Achievement Test, Fifth Edition; ToPF: Test of Premorbid Functioning; WIAT-4: Weschler Individual Achievement Test, Fourth Edition; HART: Hopkins Adult Reading Test; NAART: North American Adult Reading Test; TMT: Trail Making Test; WAIS-IV: Weschler Adult Intelligence Test, Fourth Edition; PSI: Processing Speed Index; SDMT: Symbol Digit Modalities Test; CPT 3: Conners' Continuous Performance Test Third Edition, SCWT: Stroop Color Word Test; D-KEFS: Delis-Kaplan Executive Function System; CLOX: Executive Clock Drawing Test; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; JLO: Judgment of Line Orientation Test; RCFT: Rey-Osterrieth Complex Figure Test; HVOT: Hooper Visual Organization Test; NAB: Neuropsychological Assessment Battery; BNT: Boston Naming Test; HVLT-R: Hopkin's Verbal Learning Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; CVLT-3: California Verbal Learning Test, Third Edition; WMS-IV: Weschler Memory Scale, Fourth Edition; AMI: Auditory Memory Index; VMI: Visual Memory Index; BVMT-R: Brief Visual Memory Test-Revised; WCST: Wisconsin Card Sorting Test; CANTAB: Cambridge Neuropsychological Test Automated Battery; CCT: Cognitive Competency Test; ERT: Emotion Recognition Test; TASIT EET: The Awareness of Social Inference Test Emotion Evaluation Test; MET: Multifaceted Empathy Test; EQ: Empathy Quotient; GPT: Grooved Pegboard Test; FTT: Finger Tapping Test; B-SIT: Brief Smell Identification Test; AST: PHQ-9: Patient Health Questionnaire; PROMIS: Patient-Reported Outcomes Measurement Information System; BDI-II: Beck Depression Inventory-Second Edition; BAI: Beck Anxiety Inventory; GAD-7: 7-item Generalized Anxiety Disorder Scale; GAI: Geriatric Anxiety Inventory; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index; SD: Sleep Disturbance; SRI: Sleep-related Impairment; ISI: Insomnia Severity Index; FrSBe: Frontal Systems Behavior Scale; BIS-11: Barratt Impulsiveness Scale Version 11; AS: Apathy Scale; NPI-Q: Neuropsychiatric Inventory Questionnaire; PBA-s: Short Problems Behavior Assessment for Huntington Disease; HD-CFRS: Huntington's Disease-Cognitive Functional Rating Scale; FAQ: Functional Activities Questionnaire. WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0.

greater HD-related symptom severity, consistent with prior research showing that patients with more advanced cognitive impairment are predisposed to high false positive rates (Duff et al., 2011; Hook et al., 2009; Maiman et al., 2019; Teichner & Wagner, 2004). A further important consideration in HD PVT interpretation is that neurobehavioral symptoms, such as apathy, may interfere with engagement in testing. As such, previously established cutoff values for passing PVTs may need to be altered in the HD population, although further research is required.

A further consideration in the interpretation of PVT results in HD is the potential impact of neurobehavioral symptoms, such as apathy, on engagement during testing. However, recent findings challenge the notion that apathy significantly increases the risk of false-positive classification on PVTs. A study examining PVT performance in a mixed clinical sample, including individuals with various neurological disorders (i.e. as dementia, mild cognitive impairment, and Parkinson disease), did not find a significant

relationship between failure on the PVTs and the presence of clinical levels of apathy (Dandachi-FitzGerald et al., 2020). This suggests that apathy may not be a strong contributing factor to false-positive classifications on PVTs in HD. Additionally, the study demonstrated that adjusting cut-scores for certain PVTs, such as the Dot Counting Test (DCT) and the Test of Memory Malingering (TOMM), may enhance their accuracy in detecting suboptimal engagement or poor effort. The DCT showed a higher failure rate compared to the TOMM, possibly due to differences in the cognitive load of these tests. Raising the cut-scores for the DCT resulted in a lower false-positive failure rate, while the TOMM maintained satisfactory accuracy with adjustments to the cut-score.

These findings suggest that adjusting the cut-scores for specific PVTs, such as the TOMM and DCT, may improve their accuracy in detecting suboptimal engagement or poor effort in patients with HD. However, it is important to note that further research is needed to determine the optimal adjustments for cut-scores in the HD population. We strongly advocate for the use of PVTs throughout the course of HD, including the pre-symptomatic stage. The evaluation process for pre-symptomatic HD patients involves multifaceted considerations, including concerns about future prognosis, potential social and occupational implications, and personal expectations. These factors contribute to a complex interplay of motivations and perceptions of performance. While it may not be immediately apparent, the presence of strong incentives to exaggerate deficits or perform suboptimally cannot be ruled out entirely, as these motivations can influence individuals' approach and engagement during testing, potentially affecting their performance on PVTs. By implementing this practice, clinicians can effectively navigate the complex interplay of motivations and perceptions while maintaining the highest standards of assessment integrity.

It is also critical to attend to neuropsychological battery duration, as many extensive batteries take too long, especially in the context of bradyphrenia in HD, and lead to confounds from fatigue on test performance. As mentioned, selection of tests with consideration of their motor demands is also essential; tests with speeded responses, or requiring fine dexterity are tiring for people with HD and other movement disorders, and as such should be either minimized or limited to manage patient burden and ensure a clear picture of cognitive function emerges.

Once a clinical diagnosis of HD-associated or associated neurocognitive disorder has been established, full batteries may not offer incremental clinical utility to the referral question—e.g. in a circumstance of HD with Major Neurocognitive Disorder. Instead, commenting on the course of functional impairment in daily life, and/or behavioral/psychiatric symptoms, may be more useful in treatment planning. For follow-up assessment, alternate forms should be considered if available, especially if the interval is less than a year.

Part 3: diagnosis

The MDS recommended application of the DSM-5-TR Neurocognitive Disorder diagnostic criteria in the setting of HD (American Psychiatric Association, 2013) but did not go beyond discussing the Mild and Major subtypes. Here we offer an expanded operationalization with additional considerations that commonly occur in the clinical

application of this nosology. Table 2 presents the operationalization of Mild and Major NCD due to Huntington disease. The distinction between Mild and Major NCD depends on 1) the magnitude of cognitive impairment, and 2) the extent of impact on functional independence. A clinical distinction of with or without behavioral disturbance is optional, and we recommend that such a distinction be made if the clinician has sufficient information from observation and patient/collateral report (neuropsychiatric questionnaires and/or report of specific behavioral changes including perseveration, irritability, psychosis). We note, however, that behavioral disturbance is considered only outside the context of delirium or other well-established premorbid psychiatric conditions, such as major depression or schizophrenia. The degree of confidence that a behavioral syndrome represents a neuropsychiatric manifestation of HD-related pathology may increase for phenotypes that are relatively rare in the general population (e.g. psychosis). We also support considering including in the clinical diagnosis the presence of a complete or partial anosognosia syndrome as an HD-related behavioral disturbance. Of note, in the soon-to-be released ICD-11, and criteria for Mild Cognitive Disorder (MCD) and dementia syndromes closely align with the Mild and Major NCD criteria of the DSM-5-TR, respectively. Similar to DSM-5-TR, the ICD-11 text indicates that an MCD/dementia disorder diagnosis is not indicated in cases where cognitive symptoms are favored as secondary to primary psychiatric disorder, sleep disorder, delirium, or another medical condition that does not have an empirically supported neuropathophysiological mechanism implicated as causal for the cognitive symptoms. That said, the ICD-11 criteria acknowledge manifestations of behavioral dysfunction in neuropsychiatric presentations may be taken into diagnostic consideration. Thus, we would propose that either DSM-5-TR or ICD-11 nosology may be employed in applying our proposed criteria to clinical diagnosis of cognitive and behavioral symptoms of HD.

An important consideration in diagnosis of neurocognitive disorder in HD is the high base rate of comorbid medical complications, such as moderate-to-severe TBI (e.g. falls, MVCs, assaults), respiratory arrest or hypo/anoxia (e.g. overdose, suicide attempt), and direct neurological insult secondary to substance consumption. In such cases, a diagnosis of Mild or Major Neurocognitive Disorder due to Multiple Etiologies, with or without behavioral disturbance, is warranted. Importantly, the neurocognitive syndrome in HD is characterized by a gradual and progressive decline rather than a sudden or stepwise picture; therefore, detailed histories should be used to support this gradual, progressive picture, or suggest alternative diagnoses that may be more accurate. Finally, Unspecified Neurocognitive Disorder is indicated in the presence of clinically significant symptoms when a full clinical evaluation is unavailable to support more specific diagnostic determination, such as in settings with limited neuropsychological resources or expert providers.

Several circumstances warrant a conservative application of either DSM-5 or ICD-11 NCD criteria. First, when multiple etiological considerations for cognitive impairment exist, making a definitive NCD diagnosis should be postponed until a more comprehensive clinical evaluation has been completed, and any treatable/reversible causes of impairment have been managed. Similarly, when patients show fluctuating or mild cognitive symptoms, neuropsychologists should wait to assign an NCD diagnosis until other treatment/interventions have been pursued, or clinical signs demonstrate a

Table 2. DSM-5 Mild and Major Neurocognitive disorder due to Huntington disease.

DSM-5 Syndrome	DSM-5 Criteria	Diagnostic Feature	Associated Features	Functional Consequences

Mild or Major Neurocognitive Disorder Due to HD	• Criteria for mild or major neurocognitive disorder was met (see below)
	• Insidious onset and gradual progression
	• Clinically established HD or risk for HD based on family history or genetic testing
	• Neurocognitive disorder is not attributable to another medical condition and is not better explained by another mental disorder
		• Progressive cognitive impairment is a core feature of HD, with early changes in executive function (i.e. processing speed, organization, and planning) rather than learning and memory
		• Cognitive and behavioral changes often precede the emergence of typical motor abnormalities of bradykinesia
		• Diagnosis of definite HD given in the presence of unequivocal, extrapyramidal motor abnormalities in an individual with a family history of HD, or genetic testing showing a CG trinucleotide repeat expansion in the HTT gene (chromosome 4)
			• Frequent
			  • Depression
			  • Irritability
			  • Anxiety
			  • Apathy
			  • Obsessive-compulsive symptoms
			  • Sleep disorder
			• Rare
			  • Psychosis
				• In prodromal stage and early illness, occupational decline is most common
				• Emotional, behavioral, and cognitive aspects of HD (e.g. disinhibition and personality changes) are highly associated with functional decline
				• Cognitive deficits that contribute to most functional decline include processing speed declines, inattention, and initiation difficulties
				• Given the age of onset, HD can greatly affect social, occupational, and family life
				• As the disease progresses, disability from motor symptoms becomes more apparent, as well as disability from continued cognitive impairment

Differential Diagnosis

- **Criteria for a mild neurocognitive disorder:**
  - Modest cognitive decline from prior level of performance in one or more cognitive domains based on 1) concern from the individual, informant, or clinician; or 2) modest impairment on neuropsychological assessment.
  - The cognitive deficits do not interfere with everyday independence.
- **Criteria for a major neurocognitive disorder:**
  - Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domain based on 1) concern from the individual, informant, or clinician; or 2) substantial impairment on neuropsychological assessment.
  - The cognitive deficits are functionally limiting (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living).
- For both a major or mild neurocognitive disorder diagnosis, these cognitive symptoms do not occur in the context of a delirium and are not better explained by another mental disorder.
- Early symptoms of HD may include emotional lability, irritability, or compulsive behaviors that may initially suggest another mental disorder. Genetic testing or developmental of motor symptoms will increase diagnostic clarity.
- Early HD symptoms, such as executive dysfunction and impaired psychomotor processing speed, can resemble other underlying etiologies for cognitive disorders (e.g. Parkinson's disease, vascular dementia).
- HD is not the only consideration in the context of chorea, such as Wilson's disease or drug-induced tardive dyskinesia.

Note. Adapted from DSM-5.

clearer progressive picture. For example, neuropsychiatric changes, such as depression and anxiety, do not reliably track with disease progression or severity of cognitive deficits, and if these are severe or untreated, a cognitive diagnosis should be deferred. This rationale stems from the fact that a NCD due to HD diagnosis presently implicates disease manifestation, and, in the near future the field is thought to be shifting toward inclusion of non-motor symptoms be considered in diagnosis of a manifest HD condition, which we touch on later in this section. Such a diagnosis may trigger changes to patient identity, clinical trial eligibility, disability, legal capacities in certain settings, etc. Thus, assigning the NCD diagnosis to HD etiology should be made when there is more than probable diagnostic confidence.

Special consideration is needed when a patient exhibits only subtle cognitive deficits on exam yet experiences significant functional impairment due to neuropsychiatric symptoms. In some cases, this occurs when patients have social cognitive deficits causing significant functional impairment, which are often not detected during formal cognitive testing. In such situations, a diagnosis of Major NCD may be warranted, as is often observed in early Frontotemporal Dementia-behavioral variant (bvFTD), in which neuropsychological evaluation is within normal limits, but the patient is nonetheless incapacitated due to behavioral deficits manifesting primarily in the social environment.

The HSG-NPWG offers our recommendations for incorporating cognitive assessment in the context of clinical diagnosis of cognitive and behavioral symptoms of HD, specifically in the context of the recommendation of the MDS Task Force for the diagnosis of HD. We recognize, however, the continued development of diagnostic processes, and the varying purposes served by diagnostic frameworks. As such, we have yet to examine how cognitive assessment may be able to contribute to a new staging system described for HD, the HD Integrated Staging System, or HD-ISS (see Figure 2). The HD-ISS is a novel staging system generated by a team of researchers associated with the HD Regulatory Science Consortium, or HD-RSC, an industry-academic consortium of the precompetitive Critical Path Institute. The HD-ISS is for people with CAG repeats of 40 or more, excluding juvenile HD, and captures disease stages for the full lifespan. The staging system classifies patients based on prognostic findings that cluster together to inform critical disease stage transitions, referenced to healthy control values, and delineates the following stages:

Stage 0: CAG greater than or equal to 40
Stage 1: CAG greater than or equal to 40, and biomarker of pathogenesis
Stage 2: CAG greater than or equal to 40, a biomarker of pathogenesis, and sign/symptom
Stage 3: CAG greater than or equal to 40, a biomarker of pathogenesis, and sign/symptom, and functional change. Stage 3 can be further subdivided into mild, moderate, and severe, based on the extent of functional decline.

According to the HD-ISS, a person is designated as Stage 0 from birth, solely based on their expanded CAG. Once the first sign of HD can be observed in the form of a biomarker for pathogenesis, such as volumetric magnetic residence imaging evidence of caudate or putamen volume loss, they are considered to be at HD-ISS Stage 1. HD-ISS Stage 2 is designated once a motor (i.e. UHDRS Total Motor Score) OR cognitive (i.e. Symbol Digit Modalities Test) measure is determined to be abnormal. Stage 3 is

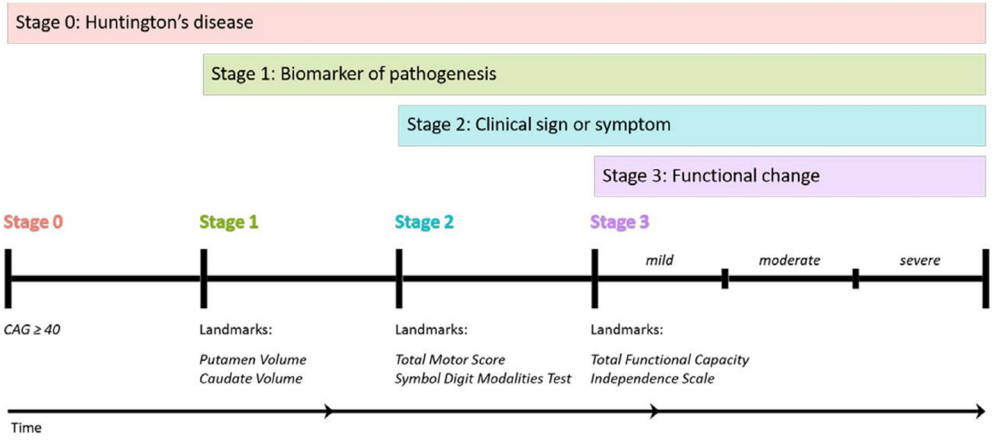

Figure 2. HD-ISS staging framework.
Note. Image is used under open-source agreement of the associated publication, with acknowledgement to Tabrizi et al. (2022).

designated once there is evidence of decline in functioning, i.e. on the Independence Scale or the Total Functional Capacity Scale of the UHDRS. Details for how cutoffs were referenced to healthy control distributions on these variables are available in the HD-ISS introduction publication (Tabrizi et al., 2022). How the HD-ISS plays out in the HD diagnostic space, and whether more specific recommendations for neuropsychologists in the context of this system can be made, is a topic of ongoing.

The NPWG's current perspective supports a modification of the model Reilmann et al. (2014) outlined for clinical application. Specifically, assigning genetically confirmed carriers presymptomatic, prodromal, or manifest HD diagnoses based on both motor and non-motor features, with functional status delineating mild, moderate, and severe manifest disease stage. We would argue that the non-motor features should include consideration of behavioral/psychiatric features that have low incidence in the general population, or, in concert with progressive motor symptoms and cognitive deficits increase confidence for the probable etiology being HD neuropathology. In this model, neuroimaging and additional diagnostics would be indicated to rule out alternative etiologies for the observed symptoms but would not be a required component of diagnosis. Were this approach widely accepted in clinical practice, the implications of a genetic carrier agreeing to a neuropsychological evaluation would need to be clearly discussed, as atypical findings may result in a diagnosis of prodromal or manifest HD symptoms, even in the absence of motor signs.

Part 4: clinical recommendations

Neuropsychologist recommendations in the context of a patient with suspected or confirmed HD genetic expansion extends well beyond clinical decisions of neurocognitive disorder diagnosis and consideration of pharmacological and non-pharmacological interventions. Recommendations may also include genetic counseling, capacity concerns, vocational issues, disability, and psychoeducation.

Pharmacological interventions. Cognitive function is a primary focus in treatment planning, but for HD, we have very limited options for addressing cognitive decline, despite the identification of several novel targets in animal models (Puigdellívol et al., 2016) and recent development of a potential oral therapy for cognitive disorders associated with HD (SAGE-718; ongoing Phase 2 clinical trial). Patients in the prodromal stage of HD commonly request stimulant medications; however, no empirical studies support their therapeutic effectiveness in HD (Beglinger et al., 2009), and these medications are associated with a host of side effects relevant to HD, including irritability, insomnia, and the exacerbation of subtle motor agitation. One study, which looked at the effects of the stimulant modafinil on mood and cognition, showed no improvement in mood and cognitive functioning, along with a worsening of cognitive function, specifically in visual recognition and working memory performances (Blackwell et al., 2008). Other stimulant medications, such as atomoxetine and methylphenidate, can either exacerbate motor symptoms or have no effect on motor, cognitive, or psychiatric symptoms (Krishnamoorthy & Craufurd, 2011). VMAT-2 inhibitors were found to not improve cognitive functioning (Huntington Study Group, 2006), with similar findings for AChEI-class medications (Vattakatuchery & Kurien, 2013); antidopaminergic medication was found to improve chorea and irritability but adversely affect cognition (Harris et al., 2020). Treatment of psychosis and mood symptoms in HD patients with off-label aripiprazole can be beneficial (Brusa et al., 2009; Patrick & Ritchie, 2020), and may therefore improve concentration.

Non-pharmacological interventions. The efficacy of non-pharmaceutical multidisciplinary interventions (e.g. cognitive training, exercise, social interactions) on HD symptoms and disease progression is also promising (Cruickshank et al., 2015; Thompson et al., 2013). In a study of people with HD from Italy admitted to an inpatient unit for three weeks, participants completed respiratory, physical, occupational, and speech therapies, along with cognitive rehabilitation. Across each week, there were statistically significant improvements in their motor abilities and activities of daily living, with no further motor, cognitive, or functional decline observed over a two-year post-intervention period (Zinzi et al., 2007). In another multidisciplinary study, a small sample of patients completed a nine-month rehabilitation program (computerized cognitive training, sleep hygiene, nutrition, exercise), which found improved auditory-verbal learning and memory, attention, processing speed, and executive functioning in those who completed the intervention (Bartlett et al., 2020). At-home computer-based cognitive training is also promising; however, adherence is variable, and it may not be suitable for all HD patients; more research is required before this method can be used clinically (Yhnell et al., 2020).

Rehabilitation for HD patients must be considered in the context of clinical severity, likelihood of functional impact, and potential for treatment-response. For example, the use of rehab strategies may be influenced by agitation/irritability, anxiety, depression with or without suicidal ideation, psychotic features such as delusions, and insomnia. These typically warrant both medication and psychotherapeutic intervention, preferably with involvement of a psychiatric specialist. Comorbid conditions known to exacerbate cognitive dysfunction or impact quality of life should also be identified,

such as reversible metabolic/endocrine/infectious conditions (low B12, thyroid dysfunction, urinary tract infection), chronic pain, sleep disorders (obstructive sleep apnea, restless leg syndrome), and sensory impairment (visual acuity issues, hearing loss). These conditions warrant referral to respective specialties to help optimize the patient's overall functional status.

Psychosocial and safety considerations. Functional safety considerations are unique to each patient and circumstance, but include capacity to conduct personal legal, financial, medical affairs; safely living independently; whether concerns around driving capacity exist; and the safety of the patient and others (e.g. access to dangerous medications or firearms if suicidal, aggressive, or demented). Blanket capacity recommendations are not recommended; instead, efforts should be made to evaluate those abilities most relevant to the capacity question at hand (e.g. managing finances or health/safety concerns). Referral to physical therapy, occupational therapy, social work, and involvement of general medical practitioner is frequently the best option in these cases. In the neuropsychology setting, clinicians are sometimes requested to make recommendations to treating clinicians and/or to a court on decision-making capacity and/or the indication for guardianship. Ideally, neuropsychologists or other members of the multidisciplinary treatment team should discuss with patients the advantages of proactively working to complete advanced directives, identifying power of attorney agents, and preparing permissions for trusted financial oversight.

Neuropsychologists are also sometimes asked for input on a patient's vocational capacity and may be in a position to recommend accommodations for their patients who are still in the work force. Similarly, some may be in school and may require academic accommodations due to cognitive or psychiatric symptoms. In such cases, the neuropsychologist can be uniquely positioned to a) articulate how deficits or weaknesses identified on formal neurocognitive evaluation translate to occupational and academic skills and b) suggest appropriate accommodations. Such recommendations may seem obvious to the practicing clinician, but often need to be carefully delineated for the non-clinical reader.

Applications for disability benefits frequently lead to the need for documentation of cognitive impairments. Particularly among patients with HD, and especially among those with a cognitive-phenotype, the neuropsychological evaluation has direct and important consequences for disability determination. Neuropsychologists are trained to provide a nuanced account of the cognitive sequelae of HD, which are less readily observable by the layperson, particularly in comparison to motor signs of HD, which can be obvious to any astute observer. Moreover, neuropsychologists' training provides a strong basis for them to explain how cognitive impairments or declines may affect a patient's capacity to perform routine vocational tasks. A brief but thoughtful comment regarding subtle executive dysfunction in a construction company foreman, for example, may help a disability claim reviewer to better understand the impact of HD on a person's work performance, and in turn their vocational capacity limitations. Similarly, a disability reviewer may not immediately understand why bradyphrenia would impede a receptionist's ability to perform his/her job, but a neuropsychologist can explain the impact in a well-crafted sentence or two in the report. It can also be helpful to mention the nature and relentless course of HD, as well as the current

lack of effective treatments for cognitive symptoms, particularly for those patients who may be in the early stages of cognitive decline and whose symptoms may appear minor or even non-existent to the lay observer.

Psychosocial education is another area in which the neuropsychologist can assist the patient and family, and these needs are often considerable. If the evaluation is taking place in the context of an HD multidisciplinary clinic (e.g. HDSA Centers of Excellence in North America), there may be additional support for psychoeducational interventions (e.g. social workers, case managers). In such cases the neuropsychologist may be able to explain, at a basic level, the neurological basis of a patient's cognitive and neuropsychiatric changes. Such explanations can help the family understand that behavioral changes, which are often frustrating and difficult to manage, are the result of brain dysfunction, rather than attributable to other more modifiable factors. In the case of the solo practitioner who encounters HD in private practice, in the absence of a multidisciplinary team, it is particularly helpful to connect the patient and family with additional resources. These may include social workers, case managers, support groups, the local Huntington advocacy organization, and other community resources, which can foster functional independence and quality of life. These resources are also important for children and other family members who are currently (or may in the future be) serving in a caregiving role. Proactive legal considerations might also be discussed; for instance, patients may wish to carry diagnosis/explanation cards for law enforcement.

Conclusions

Neuropsychological evaluation is critical for implementing the non-motor HD diagnostic framework. Standardized clinical approaches are important to facilitate this objective. While research batteries offer a good starting point, limitations have been identified in recent pilot attempts such as the HD-CAB, namely a lack breadth in cognitive performance measures and neuropsychiatric symptom screens for the clinical setting. This position paper offers neuropsychologists initial guidance for how to approach the neuropsychological evaluation of HD. Finally, future development of a consensus clinical battery for patients with HD would provide a unique opportunity to better define and compare neuropsychiatric and cognitive symptoms in HD expansion carriers versus non-expansion carriers to establish cognitive and psychiatric phenotypes of HD.

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