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Cognitive Impairment in Huntington Disease: Diagnosis and Treatment

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Abstract Cognition has been well characterized in the various stages of Huntington disease (HD) as well as in the prodrome before the motor diagnosis is given. Although the clinical diagnosis of HD relies on the manifestation of motor abnormalities, the associated impairments have been growing in prominence for several reasons. First, research to understand the most debilitating aspects of HD has suggested that cognitive and behavioral changes place the greatest burden on families, are most highly associated with functional decline, and can be predictive of institutionalization. Second, cognitive impairments are evident at least 15 years prior to the time at which motor diagnosis is given. Finally, cognitive decline is associated with biological markers such as brain atrophy, circulating levels of brain-derived neurotrophic factors, and insulin-like growth factor 1. Efforts are now underway to develop valid and reliable measures of cognition in the prodrome as well as in all stages of HD so that clinical trials can be conducted using cognitive outcomes.

Keywords Mild cognitive impairment · Dementia · Cognitive impairment · Diagnosis · Huntington disease · Prodrome of HD

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Introduction

Huntington disease (HD) is a hereditary neurodegenerative disorder caused by an expansion of a repeating CAG triplet series in the huntingtin gene on chromosome 4, which results in a protein with an abnormally long polyglutamine sequence [1]. The normal function of the huntingtin protein is not known. Neuropathology indicates loss of medium GABAergic spiny neurons, sparing of large cholinergic interneurons, and specific neuronal loss in layers V and VI of the cerebral cortex [2, 3]. Morphometric analyses from MRI suggest marked atrophy in the striatum, thinning of the cortical ribbon, and evidence of white matter volume loss [4–6].

HD has long captivated significant interest in academic medicine and clinical health care due to its autosomal dominance, tripartite clinical features (motor, psychiatric, and cognitive), and tragic life circumstances witnessed by its victims. Interested readers are referred to two excellent review papers published within the past year [7, 8]. The current review emphasizes the progress made in cognitive aspects of HD over the past year with an emphasis on implications for diagnosis and treatment.

Diagnosis of HD

The diagnosis of HD remains a clinical diagnosis. It is based on a neurologic evaluation with the manifestation of an unequivocal extrapyramidal movement disorder in conjunction with a positive genetic test for the HD CAG expansion or a confirmed family history of HD. Those who are found to have the HD gene expansion through genetic testing, but who do not yet exhibit significant motor signs, are said to be in the prodromal phase of HD [9, 10]. Despite

a strong relationship between the CAG repeat number and the age at which HD symptoms begin, the association is not sufficiently uniform to enable the prediction of a specific onset age for an individual. In addition, knowledge of the CAG repeat number does not help the patient or physician to know what HD-related symptoms the person is going to develop, how severe they will be, or how rapidly the disease will progress [11].

Data from prospective longitudinal studies have been analyzed to determine what clinical and/or biological measures most contribute to a motor diagnosis of HD. Available studies to date suggest that a variety of additional data are predictive of pending diagnosis, including cognitive decline, subtle motor signs, reduced white matter volumes, and subjective complaints of noticeable change [12–15]. Aylward et al. [16] have shown that striatal volume is reduced by 50% at the time of motor diagnosis. Despite burgeoning evidence of cognitive and psychiatric expressions of disease up to 15 years before the motor manifestation, no diagnostic criteria has yet been established for consideration of these features.

Cognitive Diagnoses in HD

There is no accepted cognitive battery for the cognitive assessment of HD although most HD centers rely on the Unified Huntington Disease Rating Scale (UHDRS) [17], which incorporates the Symbol Digit Modality Test, the Stroop Color Word Test, and a Verbal Fluency test as part of a comprehensive examination. Before any interpretations of cognitive assessment can be made, however, demographic and premorbid characteristics must be considered. For instance, estimates of premorbid intellect are critical to inferences made about cognitive decline. Two new studies were published in the past year addressing the challenge of making estimations of premorbid intellect in patients with HD. Carlozzi et al. [18] examined performance on the American National Adult Reading Test and the two-subtest version of the Wechsler Abbreviated Scale of Intelligence and demonstrated adequate reliability and validity for each, although both tests showed decline throughout the HD course. O'Rourke et al. [19] compared test-based versus demographic-based estimates of premorbid intellect in HD patients and reported that demographic-based estimates were less related to disease progression and may reflect a more valid indicator of prior cognitive capacity.

The diagnosis of mild cognitive impairment (MCI) [20] has been growing in popularity due to its utility in the prediction of poor cognitive outcomes. Duff et al. [21] applied conventional criteria for MCI to a large sample of prodromal HD and reported that at least 38% of prodromal HD showed impairment on standardized assessment. A prospective longitudinal study will be critical to determine whether MCI might be a useful concept in the early detection of HD as it has proven utilitarian in other neurodegenerative disorders [22].

The prevalence of dementia in HD varies widely depending upon the criteria applied. Peavy et al. [23••] argue that the importance of designating criteria for diagnosing dementia has been underestimated and that appropriate criteria for dementia specific to HD have implications for clinical treatment, research, caregiving, and decision making. Peavy et al. show that speed of processing, initiation, and attention measures better defined the onset of functional decline in HD than traditional definitions created for Alzheimer disease, which require memory deficits. Strict application of dementia guidelines developed for other neurodegenerative diseases appear inappropriate for HD. Peavy et al. propose the following definition for dementia in HD: cognitive impairment in at least two areas of cognition in the context of impaired functional abilities and a deteriorating course. Application of this definition showed excellent classification in a clinical sample and was consistent with current literature as well as neuropathological understanding of HD.

Screening instruments have long been used to screen for dementia in HD. Although both the Mini-Mental State Exam and the Dementia Rating Scale have been used for the characterization of HD dementia, a recent report by Mickes et al. [24] shows that the Montreal Cognitive Assessment (MoCA) offers greater utility for the screening of cognitive impairment in HD. Further research will be needed to provide longitudinal, clinical, and functional outcomes of the MoCA in HD.

Recent Cognitive Findings in HD

Cognition has now been well characterized in the various stages of the disease as well as in the prodrome, decades before the motor diagnosis is given. Although the clinical diagnosis of HD relies on the manifestation of motor abnormalities, the associated cognitive and behavioral impairments have been growing in prominence for several reasons. First, research to understand the most debilitating aspects of HD has suggested that cognitive and behavioral changes place the greatest burden on HD families, are most highly associated with functional decline, and can be predictive of nursing home placement [25–27]. Second, the cognitive and behavioral symptoms/signs of HD have been shown to be evident at least 15 years prior to the time at which motor diagnosis is typically given [9, 10, 12] and are highly related to disease-specific volume loss on MRI [4, 28, 29]. As a result, efforts are now underway to develop valid and reliable measures of cognition in the

prodrome as well as in all stages of HD so that clinical trials can be conducted using cognitive outcomes.

It has become clear that much is to be gained from the cognitive study of HD. As a result, new publications in HD and cognition are emerging exponentially. Because it is not feasible to review every new publication in this growing area, studies highlighted were chosen to provide readers with a gestalt of progress made and of the needs unmet.

Table 1 shows a rank listing of the effect sizes (ES) of tasks representing the earliest cognitive indicators of HD. The earliest deficit detected is emotional recognition, which is significantly different from controls in gene-expansion participants who are more than 15 years from their predicted motor diagnosis. This finding is consistent with imaging findings showing that white matter is significantly impaired in this subgroup and with anecdotal evidence from families who report early difficulties in social relations. Within 15 years of predicted motor diagnosis there are numerous cognitive measures available to detect impairments in prodromal HD. The most robust changes are in time production followed by speed of processing, both showing large differences compared with controls matched in age, gender, education, and premorbid intellect. The next most robust group of measures includes those involving learning and working memory; they show medium to large ES. The prodromal HD groups who are most close to receiving a motor diagnosis of HD show numerous differences from controls, with ES of over a dozen cognitive tests being in the large to very large ranges. These findings offer a wealth of choices for the early detection of disease in prodromal HD patients who are less than a decade from diagnosis. Cognitive tests in this group include those mentioned above as well as smell identification, a sequential task allowing advance information to improve performances, and some familiar traditional tests such as Trail Making, Symbol Digit, Stroop, and Letter Fluency. Although Table 1 shows the tasks most likely to be used in the early detection of HD, the Circle Tracing task recently published in HD [30] and prodromal HD [31••] is likely to show competitive ES in these groups as well.

Table 2 shows a list of tasks that have longitudinal data and reports annualized change scores [32••]. Such data will be critical prior to the design of a clinical trial battery. The tests used for the testing of new treatments must show adequate change over time. Although much more longitudinal data will be needed to make informed decisions about cognitive assessments, the table provides an excellent starting point for consideration of tests. Unfortunately, this study did not find any tests that were sensitive to changes in the prodrome of HD. They did report at least three candidates for change in diagnosed HD, however, including Circle Tracing, Stroop Word Reading, and Symbol Digit Modality tests. Other longitudinal data are available but findings vary greatly. Some studies show an acceleration of decline in cognitive measures over the 15 years prior to motor diagnosis [33], whereas others suggest that only some cognitive measures show acceleration [34, 35]. Careful longitudinal study is critical to the choice of cognitive measures for clinical trials. Efforts are needed to encourage researchers to utilize a common metric to define and group HD so that study findings can be better compared across studies. To date, different definitions of

Table 1 Cross-sectional Cohen's *d* for cognitive tasks with medium to very large effect sizes

Task and variable	*d* NEAR	*d* MID	*d* FAR
Time production in alternating thumbs	−1.17	−0.61	
Speeded tapping with nondominant index finger	−1.14	−0.61	
Emotion recognition task	−1.10	−0.61	−0.26
University of Pennsylvania smell identification test	−1.04	−0.36	
Symbol digit modalities test	−0.96	−0.49	
Hopkins verbal learning test—Revised total learning	−0.95	−0.48	
Two-choice response time task	−0.80	−0.43	
Trail making test B	−0.80	−0.33	
Cued sequence task: use of information in problem solving	−0.78	−0.26	
Simple response time task	−0.77	−0.40	
Stroop color: Total correct	−0.75	−0.39	
Stroop word reading	−0.66	−0.27	
Working memory 2-back task	−0.64	−0.29	
Stroop interference	−0.62	−0.32	
Trail making test A	−0.60		
Phonemic verbal fluency total correct	−0.51	−0.29	
Working memory WAIS–III Letter–Number Sequencing	−0.51	−0.43	
Category rule-based learning task: Rule-based	−0.50		

NEAR=≤9 years to estimated Huntington disease (HD) diagnosis; MID=9–15 years to estimated HD diagnosis; FAR=>15 years to estimated HD diagnosis; All significant for Dunnett's test of mean differences in performance for each prodromal HD group compared with controls; significant tests not shown if effect sizes were <0.50.

(Adapted from Stout JC et al., Neurocognitive Signs in Prodromal Huntington Disease, Neuropsychology, Vol. 25, No. 1, 1–14 [Table 2], 2011, APA. Adapted with permission); [40••].

Table 2 Adjusted annualized change in cognitive measures with *p*-values

Task and variable	Prodromal HD	Diagnosed HD
Circle tracing w/indirect feedback	−44.3; 0.0229	−107.1; <0.0001*
Circle tracing w/direct feedback	−3.7; 0.94	−110.5; 0.0178
Stroop word reading	−0.14; 0.92	−4.75; 0.0004*
Symbol digit modalities test	−0.94; 0.19	−3.73; <0.0001*
Spot the change test	0.11; 0.51	−0.28; 0.10
University of Pennsylvania smell identification test	0.32; 0.20	−0.76; 0.0123
Speeded taping w/serial 2 s	−0.001; 0.41	−0.003; 0.0170
Time production	−0.001; 0.57	−0.0002; 0.0539
Emotion recognition task	−0.08; 0.89	−1.15; 0.0485

*significant at $p<0.01$

(Adapted from Tabrizi SJ et al., Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis, The Lancet Neurology 2011, Vol. 10, 31–42 [Table 2]. Adapted with permission); [32••].

prodromal and HD staging are making cross-study interpretations impossible.

Timing

Findings have suggested that persons with HD have difficulty with the estimation of time 15 years before motor diagnosis. Spouses often complain that their once-punctual spouse becomes frequently late and mis-estimates how long activities will take. Many studies have demonstrated impairments in the perception of time and the production of timed output in prodromal HD and HD [28, 36, 37, 38••]. The ES of the timing variability is very large (>1.17), suggesting that the difference between prodromal HD and controls is easily detected with timing measures. Most recently, Rowe et al. [38••] reported that the timing task can be repeated longitudinally and that change scores on these tasks are significant with medium effects sizes, suggesting that timing may be a suitable measure to track changes in clinical trials. These findings are consistent with those reported from animal studies showing that the timing of initiation and termination of sequential actions are dependent upon the striatum [39]. Tabrizi et al. [32••] reported change scores using a similar timing task but found no significant longitudinal ES in prodromal HD or HD. Further examination is required to better understand the discrepancy between these two important studies.

Speed of Cognitive Processing

One of the earliest and most sensitive indicators of the early signs of HD includes changes to the speed of thinking and motor skills. The person at risk for HD will begin to notice that completion of ordinary mental tasks is more tiring and takes more time to achieve the same outcome. It appears that the brain compensates for dysfunctional circuitry by using "effortful" processing to do tasks that were once automatic and by recruiting alternate areas of the brain for cognitive tasks, all of which slows processing speed. Nearly any cognitive or motor task that requires speed is sensitive to the detection and progression of prodromal HD and HD. The challenge for neuropsychologists and measurement specialists at this point is to validate the most efficient and robust measures of motor speed and cognitive speed for HD.

The PREDICT-HD study [9, 10] administered several conditions of a standard speeded tapping test to 738 prodromal HD participants. Effect sizes (ES) between various stages of HD and gene-negative controls ($n=168$) showed that speeded tapping of the nondominant index finger produced the most robust power (effect sizes > 1.14 for prodromal HD). Other tapping conditions considered were dominant index finger (ES=0.77) and alternating thumbs (ES=0.94) [40••]. Bechtel et al. [41] reported on a comparison of more sophisticated tapping measures using pre-calibrated and temperature-controlled force sensors (Mini-40, ATI) in 120 prodromal HD and 123 HD and also reported robust effect sizes (1.03 for prodromal HD and 2.37 for diagnosed HD).

It is clear from the excellent progress over the past year that speeded tapping will remain a good measure for the detection of HD, even in prodromal HD and its earliest stages. What remains to be determined is whether these tapping measures will be useful as a change marker in clinical trials and which of the various tapping measures will prove to be the most cost effective and robust for multisite clinical trial research.

Emotion

One of the earliest cognitive impairments detected in prodromal HD is the identification of which emotion is being communicated in a facial expression or from verbal intonation [42, 43]. When at-risk individuals were asked to identify whether a facial expression or verbal tone represented fear, sadness, or disgust, performances were significantly impaired. It is important to note that understanding of emotions and memory for emotions is intact; it is the identification of emotion based on the complex processing of the cue that becomes difficult. Henley et al.

[44] replicated the defective emotion recognition in early HD and reported associated brain atrophy from MRI. de Gelder et al. [45] extended the deficit of emotional recognition of faces and verbal tones to include recognition of emotions expressed in instrumental body language. Most recently, Calder et al. [46••] provided a comprehensive overview and set of studies that clarify and extend underlying processes of this finding. Calder et al. artfully demonstrate that the related emotions of disgust and anger associated with social disapproval are most frequently and disproportionately impaired in HD. It is hypothesized that this early and pervasive impairment may be associated with growing difficulties in social relations.

Olfaction

It has been known for more than 15 years that the olfactory system is impaired in patients with a diagnosis of HD [47–49]. Although HD patients were able to detect the smells, they were less able to identify what the smell was. Performances on traditional memory tests were intact even when smell identification was impaired. More recently, persons in the prodrome of HD performed in the impaired range on a test of smell identification, suggesting that the olfactory system is compromised early in the disease. Recent publications of large cohorts of prodromal and early-staged HD have replicated the sensitivity of olfactory testing (using the University of Pennsylvania Smell Identification Test or UPSIT) for the detection and tracking of HD [32••, 40••].

Memory

Memory problems are a frequently reported symptom of HD. Individuals with the disease will have difficulty learning new information and retrieving previously learned information [50–52]. Although explicit learning and memory problems do exist in HD, it is likely that the implicit memory system is more compromised by HD. Implicit memories include those collections of coordinated movements and skills that allow an individual to ride a bike, play a musical instrument, and perform tasks such as driving a car. Impairment in this area affects even the ability to chew and swallow without choking. It has long been known that persons with severe amnesia or Alzheimer disease can experience defective explicit memory, such as for names and dates, while retaining implicit, or unconscious memory, such as the ability to tie one's shoes. In contrast, older memories of names and dates are often unaffected in persons with HD [53], even as they develop impairments in implicit, or unconscious, memory.

Say et al. [31••] recently replicated a key study published by Lemay et al. [30] in which participants with HD and prodromal HD were required to trace a circle under conditions with varying feedback. In one instance, participants were able to view their hand tracing directly on top of the circle and could see the accuracy of their trace, encouraging ongoing visual feedback and the opportunity for error correction. In a comparison condition, the hand was obscured and the participants could only visualize the circle they were tracing on a computer screen presented in front of them, encouraging participants to rely on proprioceptive feedback and implicit memory for the task. Findings showed that all prodromal HD and HD groups were slower than controls and that performance was less accurate than controls in the obscured hand condition. Importantly, the authors dissected the findings to separate poor performances secondary to psychomotor slowing and those due to impaired proprioceptive and implicit memory processing. This dissociation has been reported in previous papers [54, 55]. The integration of tasks using indirect or proprioceptive feedback for error correction may be important in future studies wanting to assess basal ganglia integrity. It is also likely that such tasks may be sensitive as markers of disease detection and progression in clinical trials. The Circle Tracing task recently demonstrated significant annualized change in diagnosed HD, suggesting its possible utility as an outcome measure in clinical trials [32••].

Jin and Costa [39] trained a group of mice in a self-paced sequence learning task and reported that neural activity of the striatal medium spiny neurons showed phasic changes consistent with action sequences. That is, striatal neurons indicated the starting and stopping components of the sequence but decreased during the middle phases of the sequence. These authors suggest that the basal ganglia are important in the initiation and termination of action sequences. Such findings are key to understanding the functional declines that impact persons with HD.

Attentional Deficits

Attentional deficits, affecting such processes as resource allocation, response flexibility, and vigilance, are common in both diagnosed [56, 57] and prodromal HD [58]. Recent research has suggested that poor attention in HD may be due to an inability to automatize task performance, which results in the diversion of cognitive resources to tasks that are normally automatic in healthy people [59••].

Practice Effects

Practice effects, defined as improvements in cognitive test performance due to repeated exposure to the test materials, have traditionally been viewed as sources of error. Although some clinical trialists argue that practice effects

can be "wiped out" or equalized after multiple administrations, research fails to support this conclusion. For instance, Smith and Long [60] showed that practice effects were evident in controls over an 8-year interval. Duff et al. [61] reported that practice effects accounted for up to 83% of the variance in follow-up cognitive performances, after controlling for baseline cognitive functioning. This finding has been reported for several different types of diagnostic samples and for varying test-retest intervals. Whereas some researchers consider these findings an opportunity for better prognostic indices of outcomes, many researchers consider these findings to represent a major barrier to clinical trials. Regardless of their utility, the impact of repeat administrations of any behavioral measure is critical to allow accurate and valid interpretation of clinical outcomes and research findings. Much work remains to better characterize and understand the potential impact of practice effects and how they vary by tasks and by disease type and stage. Much recent work has been conducted in experimental psychology showing that the effect of practice is multifaceted, involving an increase in rate of information processing, a decrease in response caution, adjusted response bias, a strong decrease in nondecision time, as well as components of performance improvements that further disentangle into stimulus-specific and task-related components [62].

Executive Processes

Executive processes are universally and significantly impacted in HD. HD alterations in cognition are part of a constellation of behavioral and personality changes that are sometimes referred to as the "dysexecutive syndrome" [63]. Several studies have demonstrated that patients with HD are impaired on tests that require executive functions, such as the Trail Making Test (TMT) [64••], Wisconsin Card Sorting Test (WCST) [65], Symbol Digit Modality Test [12], the Stroop Color Word Test [56, 66], the Verbal Fluency tests [67], and clinical rating scales of executive dyscontrol [68–70]. One of the most salient advancements in the cognitive HD literature over the past year is the growing effort to dissect neuropsychological performances into relevant cognitive constructs. These efforts are critical to better understanding the etiopathophysiology of HD as well as improving the design of clinical trials.

O'Rourke et al. [64••] dismantled the TMT in a sample of 767 participants with prodromal HD to determine the contributions of motor, psychiatric, and cognitive changes to TMT scores. Eight traditional and derived TMT scores were also evaluated for their ability to differentiate prodromal HD participants closer to estimated age of diagnosis from those further away and prodromal HD individuals from healthy comparisons. Results indicate that visuoperceptual processing primarily contributes to part A, and executive functioning contributes to part B. Motor signs only mildly affected part A, and psychiatric symptoms did not affect either part. Additionally, TMT scores differentiated between healthy comparisons and prodromal HD individuals as far as 9 to 15 years before estimated diagnosis. In participants manifesting prodromal motor signs and psychiatric symptoms, the TMT primarily measures cognition and is able to discriminate between groups based on health status and estimated time to diagnosis.

Communication

Communication, or the transfer of information from one person to another, requires a complex integration of thought, muscle control, and breathing. HD can impair all three of these functions. The most prominent language difficulties in people with HD are 1) speaking clearly (articulation), 2) starting conversation (initiation), and 3) organizing and understanding what's coming in and going out (comprehension of discourse). Speed of cognitive processing can impact all of these processes necessary for effective communication. Hartelius et al. [71] reported that the primary concern reported by HD patients was the increased effort and concentration demanded to communicate and noted that high speed and initiation of output were primary detriments in conversing.

As HD progresses, phrase length decreases, and pauses in speech output are extended [72]. Regardless of increasing impairments in speech production, other language functions remain relatively intact, including syntactic structure, content, and the integrity of word associations [73]. One recent study suggests that in complex discourse tasks, individual differences in cognitive capacity are likely to contribute and override other differences related to stage of disease [74]. Even in later stages of the disease, language comprehension may remain when the ability to speak is significantly diminished. This fact is important to communicate to family members, staff at care facilities, and other health care professionals. Even if a patient cannot express herself, it is likely that she can understand what is being said. Saldert et al. [74] suggest that early assessment and determination of language capabilities can assist with communication throughout the progression of disease. Talking mats are recommended to support communication in persons with HD [75].

Awareness

Awareness of one's own actions and feelings appears to be impaired in at least one third of HD patients [76–80]. Although not universal, this perceptual impairment can be associated with significant problems in daily life. Ho et al.

[80] examined HD patients' ratings of their own dysexecutive behavior and their ability to rate the behavior of a person other than themselves. Patients consistently underestimated the degree of their own dysexecutive behavior, but not of their caregivers. This suggests that patients were able to more accurately assess a third party than their own dysexecutive behavior, strengthening confidence that deficit observed was specific to self-awareness.

Hoth et al. [81] extended these findings to show that HD patient self-ratings were not significantly associated with their actual performance on clinical measures, whereas collaterals' ratings of the patients were associated with the results of the neurologic examination and cognitive testing. Patients overestimated their competency in all domains that were examined, including behavioral control, emotional control, and activities of daily living. Furthermore, patient unawareness (including both under- and overestimation of competence) was correlated significantly with failure to maintain set on the WCST. Inability to maintain set was associated with poorer patient self-awareness, consistent with one previous study in HD that found a relationship with WCST perseverative errors. Most recently, Duff et al. [68] showed unawareness in a large cohort of prodromal HD participants. Findings suggest that reporting of executive dysfunction is more accurate in prodromal HD who are furthest from predicted motor diagnosis, but awareness diminishes as proximity to motor diagnosis nears. Comparisons between persons in the prodrome of HD and their companions showed that discrepancy between the pairs of raters increased with increasing proximity to motor diagnosis.

Treatment

There is currently no cure or treatment that can halt, slow, or reverse the progression of the disease. Current treatment guidelines are based on case studies and anecdotal evidence. Several clinical trials [82, 83] are investigating means to alleviate or reduce symptoms and slow progression in clinically diagnosed as well as prodromal HD (http://www.hdtrials.org). Nearly all clinical trials in HD to date have used a total motor score and a measure of functional capacity as primary and secondary outcomes. More recently, Beglinger et al. [84] conducted clinical trials with cognitive, psychiatric, and new functional capacity outcomes. Research has suggested that traditional outcomes designed for diagnosed HD may lack sensitivity for the earlier HD and prodromal HD persons now available for clinical trials. Efforts are currently underway to develop and validate new outcome measures for clinical trials in early HD [85–89]. The validation of new measures for mood and cognition will be critical to efforts to better treat HD. Recent publications have shown that circulating levels of brain-derived neurotrophic factors correlate with mood, cognition, and motor function in HD and might serve as a marker of treatment success [90]. Additionally, high insulin-like growth factor 1 is associated with cognitive decline in HD and may provide additional biomarker targets for validation of treatments [91]. Rowe et al. [92] documented that about 22% of prodromal HD are currently taking antidepressants (mostly selective serotonin reuptake inhibitors), which will need to be considered in recruitment for clinical trials.

Conclusions

Cognitive measures have excellent potential both for the early detection of HD in persons with genetic risk and as sensitive outcomes in clinical trials. Cognitive impairment is evident decades before motor diagnosis is given, and diagnostic criteria for HD should be revisited to keep clinical practice in concert with research findings. Cognitive tools for clinical trials are needed, and much cognitive research remains to be done to assure that reliable, valid, and feasible cognitive measures are available to detect changes secondary to interventions in HD.

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