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Cognitive and Functional Decline in Huntington's Disease: Dementia Criteria Revisited

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Abstract

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The importance of designating criteria for diagnosing dementia lies in its implications for clinical treatment, research, caregiving, and decision-making. Dementia diagnosis in Huntington's disease (HD) is often based on criteria developed for Alzheimer's disease requiring memory loss. However, it is likely that other cognitive deficits contribute to functional impairment in HD before memory declines. The goal is to identify cognitive deficits that contribute to functional impairment to support dementia criteria that reflect HD neuropathology. Eighty-four HD mutation-positive subjects completed neuropsychological tests and the Unified Huntington's Disease Rating Scale Functional Independence Scale (FIS). Functional impairment was defined as 80 or below on the FIS. Speed of processing, initiation, and attention measures accounted for 70.0% of the variance in FIS ratings (linear regression) and correctly classified 91.7% of subjects as functionally impaired or intact (logistic regression). Measures of memory, motor impairment except dysarthria, neuroleptic use, and depressed mood did not improve prediction. A definition of HD dementia that includes cognitive impairment in at least two areas of cognition but does not require a memory deficit, in the context of impaired functional abilities and a deteriorating course, more accurately reflects HD neuropathology and could lead to improved research methods and patient care.

INTRODUCTION

The prevalence of dementia in Huntington's disease (HD) varies widely depending upon the dementia criteria applied. According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, a diagnosis of dementia requires decline from a previous level of social or occupational functioning. Criteria for HD dementia have been based largely on features of the dementia associated with Alzheimer's disease (AD). However, the pattern of spared and impaired cognitive abilities observed in HD is distinct from that in AD.[1, 2] HD patients typically show a profile often labeled “subcortical” and generally characterized by attention deficits, cognitive slowing, impaired planning and problem solving, and visuoperceptual and construction deficits.[3, 4] The typical phenotype for patients with dementia of AD (“cortical”), however, is characterized by prominent memory loss (i.e., rapid forgetting) with additional changes in language, visuospatial abilities, and executive functions.[1] A number of studies have attempted to identify specific cognitive, motor, and psychiatric characteristics related to functional impairment in HD including deficits in psychomotor speed,[5–7] attention and executive functions,[6, 8] and visuospatial abilities,[5] as well as motor skills coupled with timed visual tracking[9] and demographic variables.[10]

Although memory does decline in HD over time, and there are studies that have emphasized deficits in this area of cognition,[11] other studies have shown that these deficits evolve relatively later in the course of the disease[7, 12] and differ from the type of memory loss seen in AD.[1, 3, 4, 13] Snowden and colleagues demonstrated that deficits in psychomotor speed precede memory decline, supporting the notion that cognitive deficits in HD do not evolve uniformly.[7]

Use of AD criteria that requires significant memory loss will, in many cases, exclude a diagnosis of dementia in HD patients despite significant cognitive and functional decline. Guidelines for diagnosing HD dementia early in the course of the disease before memory is significantly impaired could provide among other things: 1) a marker for disease progression, 2) a better understanding of disruptive behavioral changes (e.g., increased impulsivity, poor judgment), and 3) the ability to gain access to psychosocial and financial resources to compensate for functional impairment (e.g., inability to maintain employment). A diagnosis of dementia is important due to its implications for clinical treatment, research methods, caregiving, and financial decision-making. Therefore, the goal in this study is to

identify and examine cognitive deficits that contribute to functional impairment in order to support dementia criteria that accurately reflect HD neuropathology.

METHODS

Subjects

We studied a sample of 84 subjects who were participants in the HD Clinical Research Group at the University of California, San Diego (UCSD) School of Medicine and positive for the HD gene mutation (IT15 on chromosome 4p)14 on DNA testing. We used convenience sampling to include as many clinic and predictive testing subjects as possible. A diagnosis of definite HD was made for 64 of the 84 subjects according to family history and motor abnormalities judged by a senior neurologist (JCB) to be unequivocal or likely signs of HD based on the Unified Huntington's Disease Rating Scale (UHDRS)15 standard neurological examination. A higher UHDRS total motor score indicated greater motor impairment. For the group of subjects with unequivocal or likely motor signs of HD, the mean total score was 41.2 (SD=18.4). The remaining 20 subjects showed normal motor functioning (n=8), non-specific motor abnormalities (n=9), or motor abnormalities considered possible signs of HD (n=3). For this group, the mean total motor score was 7.1 (SD=10.2). Mean CAG repeat number was 45.4 (SD=5.1). A number of subjects were taking one or more of the following medications: antidepressants (47.6%), neuroleptics (27.4%), and anxiolytics (15.5%). All participants gave written informed consent approved by the UCSD Human Subjects Protection Program.

Procedures

Neuropsychological Functioning—To assess neuropsychological functioning, we chose the Mattis Dementia Rating Scale16 (DRS) and the Stroop Interference Test.17 for several reasons. First, data from these instruments were available for the entire sample. Second, the DRS is a commonly used screening tool with relatively good sensitivity to subtle differences in overall cognitive abilities and provides scores for five distinct cognitive areas. Third, the Stroop has been widely used in HD studies and has proven to be sensitive to neuropsychological deficits found in both manifest and preclinical HD. The three conditions of the Stroop permit separation of the probable contribution of psychomotor speed from the executive function of response inhibition. Finally, both the DRS subtests and the Stroop minimized the potential for motor skills to influence test performance. In all cases a trained psychometrist administered the neuropsychological tests. Descriptions of the tests are as follows:

1) The Mattis Dementia Rating Scale is a 144-point measure of global cognitive functioning composed of five subscales: attention (37 points), initiation (37 points), construction (6 points), conceptualization (39 points), and memory (25 points).

2) The Stroop Interference Test includes three timed conditions that measure speed of processing and the ability to inhibit competing responses. Color Naming requires naming the colors of blocks presented horizontally. Word Reading requires reading color words printed in black ink, and the Interference condition, naming the ink color of color words while inhibiting word reading. The number of correct responses (including corrected responses) in 45 seconds determines the score in each condition.

Functional Assessment—We administered the UHDRS Functional Independence Scale (FIS) and Total Functional Capacity (TFC) scale. Both provide measures of independence in instrumental and basic activities of daily living (ADLs), and for both, lower scores indicate greater impairment. The FIS scale yields a rating from 0 to 100 and is an assigned rating

based on 25 questions (yes /no) that query ability to perform daily activities independently. The TFC score ranges from 0 to 13 based on five questions concerning occupation, finances, domestic chores, ADLs, and care level. Since many of the study participants were in early stages of HD with only mild functional impairment, we selected the FIS as the primary measure of functional abilities to allow for a more detailed assessment based on distinct questions for specific daily activities (e.g., maintaining accustomed employment, driving a car, managing finances, performing specific aspects of basic hygiene and household chores). In most cases, a family member or study partner who knew the subject well was present to provide or confirm information concerning functional abilities. We chose an FIS rating of 80 or below to signify functional impairment, since a score of 80 indicates a decline from pre-disease level of employment, impaired performance of household chores, and possibly difficulty managing finances. We felt that most clinicians would agree that functional impairment at this level and below would be consistent with the concept of dementia.

Motor Functioning—In addition to the UHDRS FIS and TFC scale, a senior neurologist (JCB) administered the UHDRS standard neurological examination to assess motor functioning. This evaluation provides individual scores on specific motor measures (e.g., bradykinesia, dystonia, chorea), as well as a total motor score (range: 0–124).

Depressed Mood—The UHDRS rating of depressed mood is based on reports of the subject and informant, as well as the clinician's impression. Both frequency and severity are rated on 4-point scales, with frequency ranging from `never' to `most all the time' and severity ranging from `no mood disturbance' to `severe, significant suffering' due to mood. The score is the product of frequency and severity ratings.

Statistical analysis—To guide selection of independent variables most likely to predict FIS ratings, we examined the extent to which the functional ratings were correlated (Pearson) with neuropsychological variables. All neuropsychological variables (i.e., Stroop Color Naming, Word Reading and Interference, all five DRS subscales) were significantly correlated with the FIS rating, but the correlation between Stroop Color Naming and the FIS rating was the most significant ($r = .79$; $p < .001$). Since Stroop Color Naming was highly correlated with other cognitive measures, we employed partial correlations controlling for Stroop Color Naming to identify those measures significantly correlated with the Independence Scale, but relatively independent of Stroop Color Naming. This yielded two additional variables, the DRS Attention ($r=.39$; $p<.001$) and Initiation ($r=.39$; $p<.001$) subscale scores. We then employed a stepwise linear regression analysis to identify the extent to which cognitive measures could account for variance in functional capacity, and a logistic regression analysis to predict membership in groups coded as either functionally impaired (≤ 80) or intact (> 80) using SPSS 16.0.18 The cognitive measures included Stroop Color Naming and the DRS Attention, Initiation, and Memory subscales. We included the Memory subscale to determine whether it accounted for additional variance over and above the other three measures, since one of the study's objectives was to show that the contribution of memory deficits to functional decline in HD is less prominent than impairment in non-memory cognitive domains.

Since the TFC scale is the most commonly used functional scale in HD studies, we included an additional regression analysis to assess the degree to which scores on specific cognitive tests could account for variance in the TFC score. Finally, since motor functioning, neuroleptic use, and depressed mood could affect cognitive functioning, we added these variables to the cognitive measures in separate regression analyses to determine whether they contributed to the amount of variance explained.

RESULTS

Means, standard deviations, and ranges for demographic and clinical variables including age, education, DRS total score, FIS rating, TFC score, and the total motor score are shown in Table 1. The sample was 55% female (46/84). Based on the FIS rating, fifty-eight subjects were coded as functionally impaired (FIS ≤ 80) and 26 as functionally intact (FIS > 80).

Means, standard deviations, and ranges for the neuropsychological test scores divided according to functional impairment group (i.e., impaired or intact) are shown in Table 2. The table also lists p-values associated with the corresponding t-tests.

The stepwise linear regression showed that scores on Stroop Color Naming accounted for over half of the variance (62%) in the FIS rating ($F(1,82)=134.5$; $p<.001$). The DRS Initiation and Attention subscale scores accounted for an additional 6% and 2% of the variance, respectively. The DRS Memory variable accounted for no additional variance. Taken together, Stroop Color Naming and the DRS Attention and Initiation subscales accounted for a total of 70% of the variance (adjusted $R^2 = .69$). Table 3 shows the unstandardized regression coefficients (B), the standardized regression coefficients (β), and the value of the t-statistics and associated p-values. In the logistic regression, Stroop Color Naming score and DRS Attention and Initiation subscales correctly classified 91.7% (Chi-square=66.9; $p < .001$) of the subjects coded as functionally impaired or intact (FIS). Four subjects were misclassified as impaired and three misclassified as intact, resulting in 94.8% positive predictive value and 84.6% negative predictive value.

When these data were analyzed substituting the TFC score for the FIS score as the dependent variable in a stepwise linear regression, the results were similar. Scores on Stroop Color Naming accounted for 56% of the variance in the TFC score ($F(1,82)=104.6$; $p<.001$). The DRS Attention and Initiation subscale scores accounted for an additional 9% and 2% of the variance, respectively. Taken together, these scores accounted for a total of 67% of the variance (adjusted $R^2 = .66$). The DRS Memory subscale score accounted for no additional variance.

To evaluate the influence of motor deficits on the FIS rating, we added measures of bradykinesia dysarthria, dystonia, and chorea, as well as a composite score for eye movements (i.e., ocular pursuit, saccade initiation, saccade velocity) to Stroop Color Naming and DRS Attention and Initiation in a hierarchical stepwise linear regression with the neuropsychological variables entered in Block 1 and the motor variables in Block 2. As before, Stroop Color Naming and DRS Attention and Initiation subscales together accounted for 70% of the variance; dysarthria accounted for an additional 5%. These variables accounted for a total of 75% (adjusted $R^2 = 73\%$) of the variance in the FIS rating. When dysarthria was added to the logistic regression (Block 2) with Stroop Color Naming, DRS Attention and Initiation in Block 1, the number correctly classified as impaired improved slightly (i.e., from 94.8% to 96.5%), while the percent correctly classified as intact was slightly lower (i.e., from 84.6% to 84.0%). The Chi-square significance level ($p<.001$) was the same for both analyses.

Over one-quarter (27.4%) of the subjects was taking neuroleptics at the time of evaluation. To investigate the influence of neuroleptics on functional status (FIS), we added a coded variable (on or off medication) to Stroop Color Naming and DRS Attention and Initiation in a hierarchical linear regression with the neuropsychological variables included in Block 1 and the categorical neuroleptic variable in Block 2. As before, the three neuropsychological variables accounted for 70% of the variance ($F(3,80)=62.3$; $p<.001$); neuroleptic use accounted for no additional variance. Similarly, when the neuroleptic variable (Block 2) was

added to the three cognitive measures (Block 1) in a logistic regression, the number of subjects correctly classified on the FIS did not change.

To address the question of whether depressed mood contributed to functional ability in a subset of our sample, we included the UHDRS depressed mood score (severity × frequency) in the linear regression to predict, along with the cognitive measures, the functional rating for a subset of subjects (62 of 84 or 74%) for whom data were available. When only the neuropsychological variables were included as independent variables for this subset in the stepwise linear regression, Stroop Color Naming accounted for 53% of the variance in the FIS rating with the DRS Initiation subscale score accounting for an additional 5%. When depressed mood (Block 2) was added to the three cognitive measures (Block 1) in the linear regression, the results were the same, with depressed mood accounting for no additional variance. When depressed mood (Block 2) was added to the three cognitive measures (Block 1) in the logistic regression, the number of subjects correctly classified as functionally impaired (92.9%) and functionally intact (95%) was the same as the number correctly classified by the neuropsychological variables alone. That is, including the measure of depressed mood did not improve the accuracy of the classification.

DISCUSSION

Dementia refers to a progressive decline in cognitive abilities resulting in deficits in social and occupational functioning. This study provides evidence that cognitive measures of speed of processing and attention /initiation account for a significant amount of the variability in functional independence in a sample of individuals positive for the HD mutation. Speed of processing accounted for the largest proportion of the variance in functional ability (over 50%), with measures of attention and initiation accounting for lower, but significant percentages. This finding is consistent with other studies in which slowed cognitive processing is found to be an important, often early manifestation of disease progression.[6, 7, 19, 20] Structural and functional neuroimaging studies have confirmed that neuropathologic changes in prefrontal and subcortical structures are associated with declines in processing speed.[21, 22] While it is clear that HD patients suffer from memory loss, a number of studies have not found decline in memory to be predictive of functional capacity until relatively later in disease progression. [12, 19] In addition, findings from a number of studies support the view that impaired memory in HD results largely from the inability to initiate and carry out the systematic retrieval of successfully stored information. Like processing speed, differences in memory retrieval are more likely attributable to frontal systems.[7, 23–27] In addition, results from a study by Rohrer et al.[13] suggest that in HD, memory performance is affected by slowed retrieval largely independent of the ability to store information and motor slowing.

Results from this study and others suggest that a diagnosis of HD dementia at the point of significant functional impairment should include demonstrable evidence of impairment in at least two areas of cognition (e.g., attention, speed of processing, executive functions, visuospatial abilities, memory), but without a requirement of memory impairment. Importantly, the cognitive variables identified here as effective predictors of functional impairment can be reliably measured and for the most part are consistent with findings from previous studies and with the neuropathology of HD. In addition, the results suggest that these cognitive variables can account for a significant portion of the variance in functional capacity largely independent of neuroleptic medication use, motor dysfunction, and depressed mood.

Speed of processing measured by the Color Naming condition of the Stroop in our sample was able to account for much of the variance in the functional measure. In developing

dementia criteria for HD, it is not clear whether this construct should be considered a separate cognitive domain, although speed of processing clearly affects other domains found to be important in cognitive decline associated with HD[5, 6, 12, 19, 28–30] as well as with other prototypical "subcortical" dementias (e.g., HIV [31]). Some studies have focused specifically on Stroop Color Naming and Word Reading as useful measures of information processing speed. For example, in a study investigating cognitive impairment in patients with Multiple Sclerosis, Denney and colleagues[32] considered the more automatic color naming and word reading conditions of the Stroop to be largely independent of the more controlled processing required by the Interference condition. In another study, investigators[20] assessed the relationship between motor and cognitive indices and striatal neuron loss in HD patients in early stages and found that Stroop word reading was significantly correlated with measures of striatal degeneration (i.e., PET and raclopride C11 binding potential).

Speed of processing may go by many names, including information processing speed, cognitive or mental slowing, bradyphrenia, perceptual speed, and psychomotor speed. The Color Naming and Word Reading conditions of the Stroop Interference test could be considered tests with elements of both perceptual and psychomotor speed.[33] There are also symptoms involving slowing that are considered primarily motor (i.e., bradykinesia) or psychiatric (i.e., apathy, depression) in nature. Bradykinesia, apathy, and depression, although dissociable from cognitive slowing, may have similar or overlapping neural substrates.[34, 35] The results of our regression analyses that included a measure of depressed mood for a subset of the sample suggested that mood does not account for additional variance in the functional measure over and above that explained by cognitive variables. Nevertheless, more comprehensive measures of depressed mood and the inclusion of other behavioral attributes are needed. For example, it may be important to address the effects of apathy in HD; Hamilton and colleagues [8] found that a composite apathy /executive dysfunction behavioral index contributed to functional decline in HD patients. Finally, additional studies addressing the interactions of cognitive, motor and psychiatric symptoms related to "slowing" in HD could lead to a better understanding of common underlying or interacting neuropathology.

In this study, subjects were classified as functionally impaired if they received an FIS rating of 80 or lower. In retrospect, identification of those subjects misclassified by the logistic regression revealed that all four of the intact subjects (according to the FIS rating) misclassified in the logistic regression as impaired received an FIS rating of 85. A UHDRS FIS rating of 80 indicates that the subject can no longer engage in pre-disease level of employment, cannot perform complex household chores to pre-disease level, and may need help managing finances. A rating of 90 indicates that the subject needs no physical care if difficult tasks are avoided. Most clinicians would probably agree that a rating of 90 should not be classified as impairment associated with dementia, and that a rating of 80 should be classified as impaired. Proper classification of a rating of 85, however, is less clear and should be explored further.

We have emphasized the need for a workable definition of HD dementia taking into account the unique cognitive profile that reflects the neuropathological changes associated with HD. Our findings as well as the results of previous and future studies addressing the relationship between cognitive and functional abilities can be used to advance the process of securing a definition of HD dementia on which professionals can agree.

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Table 1

Mean, SD, and range for demographic, cognitive, functional and motor variables for total sample (n=84).

	Mean	SD	Range
Age (Yrs)	45.4	11.0	20.3–67.7
Education (Yrs)	13.6	2.7	6–20
Mattis DRS	126.4	14.0	82–144
UHDRS FIS	76.0	14.5	50–100
UHDRS TFC	7.5	3.5	1–13
UHDRS Total Motor Score	33.3	22.2	0–83

SD = Standard Deviation

DRS = Dementia Rating Scale (possible range 0 –144)

UHDRS = Unified Huntington's Disease Rating Scale

FIS = Functional Independence Scale (possible range 0 to 100)

TFC = Total Functional Capacity (possible range 1 to 13)

Possible range of UHDRS total motor scores = 0 to 124

Table 2

Mean, SD, range, and comparison of impaired and intact groups on neuropsychological measures.

		Functional Independence Scale (FIS)				
		Impaired (n=58)		Intact (n=26)		
		Mean (SD)	Range	Mean (SD)	Range	t-test p-value
Stroop Interference Test						
	Color Naming	38.2 (13.7)	10–70	66.9 (15.7)	34–95	< .001
	Word Reading	51.2 (18.9)	3–94	87.5 (21.8)	48–138	< .001
	Interference	22.0 (8.9)	0–45	39.0 (10.8)	20–61	< .001
DRS	Attention	34.2 (2.0)	27–37	36.4 (.81)	35–37	< .001
	Initiation	26.0 (7.0)	7–37	35.7 (2.1)	31–37	< .001
	Constructions	4.5 (1.5)	0–6	5.7 (.56)	4–6	< .001
	Conceptualization	34.8 (3.0)	26–39	37.3 (2.0)	31–39	< .001
	Memory	21.1 (3.1)	11–25	24.2 (.80)	22–25	< .001

SD = Standard Deviation

DRS = Mattis Dementia Rating Scale

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Table 3

Stepwise regression analysis of neuropsychological variables on the UHDRS Functional Independence Scale (FIS).

Dependent Variable: FIS					
Independent Variables	**b**	**Standard Error**	**β**	**t**	**p**
Stroop Color Naming	.39	.06	.52	6.1	<.001
DRS Initiation	.44	.18	.22	2.4	.02
DRS Attention	1.43	.61	.20	2.4	.02
				R = .84	
				R^2 = .70	
				Adjusted R^2 = .69	

DRS = Dementia Rating Scale

UHDRS = Unified Huntington's Disease Rating Scale

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