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Cognitive change in patients with Huntington disease on the Repeatable Battery for the Assessment of Neuropsychological Status

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Abstract

Huntington disease (HD) is a neurodegenerative disease associated with cognitive, motor, and psychiatric deterioration over time. Although there is currently no cure for HD, there has been a surge of clinical trials available to patients with HD over the past 5 years. However, cognitive measures have generally been lacking from these trials. A brief, repeatable neuropsychological battery is needed to assess cognitive endpoints. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) may be useful for assessing change in interventional studies or for clinical monitoring. A total of 38 patients with HD were assessed using the RBANS, other cognitive tests, and the standardized HD battery (Unified Huntington's Disease Rating Scale, UHDRS) at two clinic visits approximately 16 months apart. The RBANS Attention Index, as well as individual subtest scores on Coding, Digit Span, List Recognition, Figure Copy, and Figure Recall all declined significantly over this interval. Performance on the UHDRS cognitive tests (Symbol Digit Modalities; Stroop Color, and Stroop Word) also declined, as did functional capacity. Results suggest that cognitive changes were detected both on established cognitive tasks used in HD research and on the RBANS in patients with measurable functional decline. The RBANS provided additional information about other cognitive domains affected (e.g., memory) and may be a useful measure for tracking longitudinal change.

Keywords

Huntington Disease; Neuropsychological assessment; Memory; Dementia; Executive functions

INTRODUCTION

Huntington disease (HD) is an autosomal dominant, neurodegenerative disorder caused by a polyglutamine expansion (cytosine–adenine–guanine; CAG) on chromosome four of the IT 15 gene that codes for the production of the protein huntingtin (Group, 1993). The clinical manifestation of HD is a triad of symptoms including abnormal movements (e.g., chorea), psychiatric illness, and cognitive impairment (Paulsen, Ready, Hamilton, Mega, & Cummings, 2001a). Although striatal degeneration is the hallmark of HD-related neuropathology, more widespread subcortical and cortical involvement has been documented (Aylward et al., 1998; Aylward et al., 1994; Beglinger et al., 2005; Cudkowicz & Kowall, 1990; Nopoulos et al., 2007, Paulsen et al., 2006; Rosas et al., 2003). HD is slowly progressive with the average time from diagnosis to death approximately 16 years (Roos, Hermans, Vegter-van der Vlis, van Ommen, & Bruyn, 1993).

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HD produces the classic subcortical profile of cognitive impairment, which includes psychomotor slowing, better recognition memory than free recall, inattention, and executive dysfunction (Bonelli & Cummings, 2007 Montoya et al., 2006; Zakzanis, 1998). Longitudinal studies have shown that patients suffering from HD experience widespread cognitive deterioration in attention and executive functions, psychomotor skills, verbal fluency, memory, and working memory (Ho et al., 2003; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004; Solomon et al., 2008; Ward et al., 2006). However, the onset and progression of specific cognitive deficits are variable depending on the cognitive domain and individual differences among patients (e.g., age of onset and CAG length; Kirkwood, Su, Conneally, & Foroud, 2001). In general, speeded processing, short-term memory and retrieval, and emotional processing decline in the earliest stages of disease, and memory and language impairment occurs later (Ho et al., 2003; Montoya et al., 2006).

Because HD causes progressive impairments across symptom domains, it is important to determine the rate of change in clinical variables both to better inform clinical care (e.g., family education; disability and placement planning) and for possible use as surrogate endpoints in clinical trials. Currently there is no cure for HD and only one FDA-approved medication for patients with HD (tetrabenazine). However, over the past 5–10 years there has been a marked increase in the number of clinical trials of putative disease-modifying or symptom-reducing agents. These rarely include cognition as a primary endpoint (Bonelli & Wenning, 2006), despite the fact that cognitive and psychiatric functions are closely related to patients' independence and quality of life (Hamilton et al., 2003; Marder et al., 2000; Nehl & Paulsen, 2004; Paulsen et al., 2001b). However, with clinical trials becoming more frequent and with greater awareness and interest from the HD community in research participation, trials targeting cognition are likely in the near future. Additionally, patients with moderate cognitive impairments cannot tolerate a long battery of tests. For both clinical trials and clinical assessment, a comprehensive, yet brief, repeatable cognitive battery validated in this population would be desirable.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998) is a brief cognitive screening battery that has been used to evaluate neuropsychological functioning in a wide range of neuropsychiatric conditions; however, it has been used in only two published studies of individuals with HD (Duff, Theriault, Allison, & Paulsen, 2009; Randolph et al., 1998). In the first, 20 patients with HD were evaluated using the RBANS and were compared to patients with Alzheimer's disease (AD) and healthy controls (Randolph et al., 1998). The RBANS differentiated the groups; patients with HD performed worse on the attention and visuospatial/constructional indexes than did AD patients and worse on all five indexes than did controls. Recently, we reported RBANS performance on a larger and well-characterized sample of HD patients (Duff et al., 2009). In that sample, 75 patients with HD showed impaired performance on all RBANS indexes and 11 out of 12 individual subtests. The RBANS adequately separated patients with subcortical dementia (HD and Parkinson's disease) from those with cortical dementia (AD). To our knowledge, there are no published longitudinal reports of RBANS performance in patients with HD. The purpose of the current study is to determine whether cognitive change occurs over an average of 16 months in patients with HD on the RBANS. We also evaluated cognitive and other clinical changes across this time period using the standardized battery for HD assessment, the Unified Huntington's Disease Rating Scale (UHDRS; HSG, 1996).

METHOD

Participants and procedure

Individuals seen for a clinical visit at the University of Iowa Huntington's Disease Society of America Center of Excellence served as participants for this study (December 2002 to February 2009). All procedures were approved by the University of Iowa Institutional Review Board. Informed consent documents were signed informing the participants of the risks of the study and informing them that the data would be used for research purposes. Participants were not financially compensated. All participants included in the current analyses were diagnosed with manifest HD by a movement disorder specialist during a clinical visit. Additionally, each patient completed the UHDRS battery, which is used for both clinical and research purposes, and were classified by the motor rater with a confidence rating to represent their opinion of the likelihood that the motor signs were indicative of HD. This confidence rating is a scale from 0 (normal) to 4 (unquestionable HD, ≥99% confidence) operationally defined as the unequivocal presence of an otherwise unexplained movement disorder in a subject at risk for HD. Confirmatory molecular testing for CAG expansion is not standard clinical practice in patients with a family history and the hallmark motor signs. The diagnostic confidence level (DCL) has previously shown adequate interrater reliability in a sample of 75 clinicians (weighted kappa 0.67; Hogarth et al., 2005). Because HD is a slowly progressive disease with marked heterogeneity in clinical presentation, and often the point of exact conversion from prodrome to diagnosis is vague, we further limited patients for this analysis to those rated by the movement disorder specialist as 90% or greater confidence that they had manifest HD. This eliminated patients with soft signs (DCL = 1) to moderate motor signs (DCL = 2; 50–89% confidence). Medical history was obtained from the patients. Participants were also required to have completed the RBANS at two consecutive clinic visits, which resulted in a final sample of 38 participants.

Measures

Participants were evaluated using a standardized HD assessment tool, the UHDRS (HSG, 1996). This battery includes a motor evaluation, cognitive and psychiatric assessments, and a measure of functional capacity. A neurologist examined the participant's individual motor signs (e.g., finger tapping, chorea, dysarthria). The sum of these individual signs was the total motor score, which ranges from 0 to 124, with higher scores indicating more impaired motor functioning. The total functional capacity (TFC) score (Shoulson et al., 1979), which is derived from reports of the participant and his/her companion, quantifies a participant's ability to perform both basic and instrumental activities of daily living. This scale ranges from 0 to 13, with higher scores indicating more intact functioning. A categorical classification of disease severity is based on these total scores, grouped into 5 stages, with lower stage indicating more intact functioning (e.g., TFC scores between 13 and 11 = Stage 1 HD; between 10 and 7 = Stage 2, etc.). Psychiatric symptoms are assessed in 11 domains (e.g., anxiety, hallucinations, depression), and the score is the sum of the product of frequency and severity for 11 symptoms (Beglinger et al., 2007). The total ranges from 0–176, with higher scores indicating increased psychiatric symptoms. In addition to the other measures, three cognitive tests are part of the UHDRS: phonemic fluency, Symbol Digit Modalities, and Stroop Color and Word Test. The Symbol Digit Modalities Test (SDMT, written version) reflects the number of correct items produced in 90 seconds. Phonemic fluency reflects the number of correct words produced across three 1-minute trials. Three scores are generated on the Stroop—total number of correct words read, colors identified, and items on the interference trial in 45 s. For all cognitive tests, higher scores reflect better cognitive functioning. Participants also completed additional neuropsychological and psychiatric testing, including the Repeatable Battery for the Assessment of

Neuropsychological Status (RBANS) and the Wide Range Achievement Test–3 (WRAT–3) Reading subtest (Wilkinson, 1993). Due to time constraints, participant fatigue, lack of cooperation, and/or inability to complete the tasks presented, not all measures were administered to each participant.

The RBANS is a brief, individually administered neuropsychological battery consisting of 12 subtests, which yield five index scores and a total scale. The following domains are assessed: attention, language, visuospatial/constructional abilities, and immediate and delayed memory. All subtests were administered and scored as defined in the manual, with the exception of the Figure Copy and Figure Recall, which were scored according to revised criteria (Duff et al., 2007). The index and total scores are age-corrected standard scores (M = 100, SD = 15) and were calculated from the RBANS manual norms. Individual subtest scores are reported as raw scores. Lower scores indicate poorer neuropsychological performance. Alternate forms of the RBANS were used whenever possible. The two forms of the RBANS have been shown to be of equivalent difficulty (Randolph, 1998). In this sample, 31 out of 38 (82%) participants received the alternate form at Visit 2. The order of form given was roughly counterbalanced (20 received Form A of the RBANS at the initial assessment, and 18 received Form B. At the follow-up visit, 19 received Form A, and 19 received Form B).

RESULTS

The 38 participants in the sample had an average age of 49.53 years (SD = 11.63), 55% were male, and they had an average education of 13.54 years (SD = 1.84). Slightly more than 16 months separated the first visit (V1) and the subsequent visit (V2; M = 16.25 months, SD = 10.67). At baseline, the sample had an average WRAT–3 Reading standard score (M = 91.73, SD = 11.16). UHDRS scores suggested that the sample had abnormalities in motor functions, psychiatric ratings, cognition, and functional capacity consistent with mild to moderate HD (Table 1). Specifically, 47% of the sample fell within Stage 1 (early), 38% in Stage 2, 12% in Stage 3 (moderate), and 3% in Stage 4. No one was classified with Stage 5 HD (severe), which is consistent with the study inclusion criterion of being able to complete the RBANS. We also examined patients who did not have follow-up testing to determine whether there was a bias in the reported sample. That group of 47 patients did not differ on age, education, gender, TFC, total motor score, total psychiatric score, CAG repeat length, RBANS total or index scores, or the three UHDRS cognitive tests (all $p > .05$).

Paired sample t tests at the baseline visit and Time 2 indicated that performance declined on three of the five UHDRS cognitive scores (SDMT, Stroop Color, and Stroop Word) across 16 months (Table 1). The total functional capacity score from V1 to V2 also significantly declined ($p = .001$), indicating that during this interval, patients with HD became less functional in performing everyday tasks. Psychiatric ratings and total motor score did not change. The t tests on the RBANS scores indicated that one RBANS index score (Attention) and 5 of 12 subtest scores declined significantly from Visit 1 to Visit 2 (Table 2). Of the above subtests, 2 had skewed distributions, so Wilcoxon Signed Ranks tests were performed, and the results were similar (Picture Naming, $z = -1.43$, $p = .15$; List Recognition, $z = -2.0$, $p = .46$). Effect sizes were calculated on RBANS subtests, indexes, and total score using Cohen's d. Effect sizes are listed in Table 2 and were mainly small. The largest effect sizes were on memory measures, $d = 0.39$ (List Recognition) and $d = 0.34$ (Figure Recall), although 4 other subtests had effect sizes of similar magnitude.

DISCUSSION

HD produces cognitive deficits that generally progress from specific signs associated with frontal-subcortical pathology (i.e., psychomotor slowing, executive dysfunction) to more widespread and severe impairments characteristic of subcortical dementia later in the disease (i.e., memory impairment), although individual variations are common (Langbehn & Paulsen, 2007; Lemiere et al., 2004; Paulsen et al., 2001a; Ward et al., 2006). The standardized battery of tests developed for the assessment of patients with HD, the UHDRS, is sensitive to changes over time (HSG, 1996), but is limited in its scope to measurement of psychomotor speed, attention, and executive functions. A brief, yet comprehensive neuropsychological battery would be beneficial for clinical monitoring of these patients who are often seen annually and have difficulty tolerating lengthy testing. Additionally, the increasing number of clinical trials in HD necessitates the identification of a well-characterized and sensitive tool for brief cognitive assessments. Previous research has indicated that the RBANS is a candidate battery that has shown sensitivity in the detection of cognitive impairment in mild and moderate HD, as well as specificity in distinguishing cortical from subcortical dementias (Duff et al., 2009; Randolph, Tierney, Mohr, & Chase, 1998).

The current study adds to the existing literature by providing the first longitudinal data on the usefulness of the RBANS in HD. We provide information about cognitive change across 16 months in a clinic sample of patients with mild to moderate HD. We observed decline across the two test sessions on three of the five cognitive measures from the “gold standard” in HD assessment, the UHDRS (HSG, 1996). Specifically, notable declines occurred on the SDMT and Stroop Color and Word conditions. The Stroop Interference condition and verbal fluency did not change over this interval, consistent with other HD studies with similar retest intervals (Bamford, Caine, Kido, Cox, & Shoulson, 1995; Siesling, van Vugt, Zwinderman, Kieburtz, & Roos, 1998). Functional changes as reported by the patients and their caregivers also occurred over this interval, which lends some ecological validity to the cognitive changes observed. Motor performance worsened by 3 points, but was not statistically significant. In one other study with a larger sample ($n = 78$), average motor score worsened by about 5 points across approximately one year, and psychiatric severity did not change (Siesling et al., 1998).

In comparison to the UHDRS measures, a decline was detected on 5 of 12 RBANS subtests, including Coding, Figure Recall, List Recognition, Figure Copy, and Digit Span. Additionally, the attention index, composed of Coding and Digit Span, showed a statistically significant decline. Similar decline across 16 months would not be expected in a healthy sample. In the RBANS manual, retest data are reported for a group of 40 older adults (mean age 70 years) over a 38-week interval. Although the groups are not directly comparable due to age and retest interval differences, examination of the control change scores is helpful: total scale +5.2, immediate memory +2.8, visuospatial/constructional +8.1, language −2.3, attention +1.4, delayed memory +6.2 (subtest change scores are not presented in the manual). The only significant change in index score in our sample was on attention, and it was in the negative direction (−4.1 points). Other indexes either declined or remained stable, which is clearly a different pattern than the improvements in controls listed above. The UHDRS is heavily weighted to the assessment of psychomotor speed, attention, and executive functions. The fact that the most significant declines were observed in the same domain on the UHDRS and the RBANS (e.g., RBANS Coding and SDMT) provides evidence of concurrent validity in this sample. Although the RBANS is notably lacking in executive measures and does not contain a good analog to the Stroop test, it does provide a more broad measure of cognition than the UHDRS and captured important additional areas of decline in this sample—specifically, verbal and nonverbal memory and

visuoconstruction. Coupling the RBANS with the UHDRS measures would provide a more comprehensive assessment of neuropsychological functioning in HD.

Previous studies have demonstrated the progression of cognitive deficits during the course of disease in patients with HD (Ho et al., 2003; Lemiere et al., 2004; Ward et al., 2006). The frontal-subcortical deficits occur relatively early in the disease (Bonelli & Cummings, 2007), and these domains have been useful for tracking longitudinal change (Langbehn & Paulsen, 2007). In this sample, both the RBANS and the UHDRS tests showed declines in these areas. Memory impairment is also a common feature of the subcortical dementia produced by HD, but research has been mixed about when this deficit occurs (early vs. late) and whether recognition is relatively spared over free recall (Butters, Wolfe, Martone, Granholm, & Cermak, 1985; Ho et al., 2003; Montoya et al., 2006; Paulsen et al., 1995; Solomon et al., 2007; Zakzanis, 1998). In this sample, recognition memory on the RBANS showed significant decline across 16 months, despite a ceiling effect, suggesting that it is an important contribution to longitudinal assessment in affected patients. Visuoconstructional skills also significantly declined across 16 months, perhaps due to the high fine motor demands of the figure copy task. Indeed, motor performance has been shown to be a strong predictor of cognitive decline in other HD research (Ward et al., 2006). However, the motor changes observed in our sample between visits were mild and not statistically significant. This raises the possibility that other aspects of the figure copy task, such as the attentional and organizational elements, may have contributed to performance decline. Because our results indicate that a global measure of neuropsychological functioning did not yield a significant difference over one year, assessment of specific cognitive domains may be more sensitive to decline in HD.

Examination of the distribution of scores on RBANS subtests revealed that some of the tests produced a restricted range of scores due to floor and ceiling effects, which may have affected detectable change on either end of the distribution. The most notable ceiling effects were on Picture Naming (65% with a perfect score) and List Recognition (24%), but Line Orientation (5%), Story Recall (6%), and Figure Copy (5%) also showed minor ceiling effects. There were floor effects at V2 on List Recall (21%), Story Recall (5%), and Story Memory (3%). The latter are expected and are probably less problematic in a subcortical dementia where poor free recall is a hallmark cognitive feature. Nevertheless, naming may not be captured adequately by the RBANS in this sample, a finding that is supported by our previous study that found Picture Naming to be the only RBANS subtest not impaired in patients with HD (Duff et al., 2009).

Although this study adds to the literature by providing information about change on the RBANS, there are limitations that should be noted. First, there is likely some selection bias of this sample. Some clinic patients were not administered the RBANS if they were too impaired from either a cognitive or a motor standpoint to complete the majority of the tasks. This has likely resulted in a sample somewhat skewed toward the less impaired end of the range. However, it is assumed that future patients who require cognitive assessment would also be within this range if the RBANS is being considered as an assessment tool (i.e., those who are presymptomatic would probably require a more detailed battery to avoid ceiling effects). Additionally, clinical trials tend to recruit participants with mild to moderate HD symptomatology like those in the present sample. Second, not all participants were able to complete all tasks in the battery, so there are a small number of incomplete data sets for some tasks. Future studies should explore change over a longer interval since the average length of illness in patients with HD is 16 years, and there are presumed plateaus in decline. Similarly, assessment over more than two time points would help determine the pattern of progression, whether there is a linear decline, and which specific subtests change across time. The RBANS is likely to be useful for only a window of disease since patients will

become too impaired to complete the tasks at later stages of illness. Third, patients were not excluded for psychiatric or medical comorbidity since this is a clinical sample. There are likely psychiatric contributions to cognitive performance in these results that are difficult to disentangle from "pure HD." However, psychiatric symptoms are one of the three hallmark symptom domains of HD, and depression is particularly common, so to eliminate patients with psychiatric symptoms would bias the sample to an uncommonly restricted group (Paulsen et al., 2001a). Thus we would argue that our sample is representative of typical HD clinic patients. Finally, there are methods other than *t* tests for assessing change across time that would be useful with larger samples, such as standardized regression based formulas (McSweeny, Naugle, Chelune, & Luders, 1993).

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TABLE 1

Mean results and comparison of UHDRS clinical scores at study entry and 16-month follow-up in diagnosed HD patients

UHDRS variables	Study entry	16 months	t	p
TFC [a]	9.6 (3.2)	8.0 (2.8)	4.19	.000***
Motor score [a]	31.5 (15.9)	34.4 (14.9)	−1.23	.228
Behavioral assessment [a]	22.3 (16.4)	17.6 (19.8)	0.989	.333
Verbal fluency [b]	17.5 (10.8)	18.6 (12.4)	−0.933	.359
SDMT [b]	27.1 (10.9)	22.7 (11.2)	3.76	.001***
Stroop Color [b]	48.7 (18.2)	44.0 (17.2)	2.501	.019*
Stroop Word [b]	61.4 (20.6)	54.9(18.3)	2.874	.008**
Stroop Interference [b]	26.8 (12.0)	26.0(13.3)	0.563	.578

Note. UHDRS = Unified Huntington's Disease Rating Scale; HD = Huntington disease; TFC = total functional capacity; SDMT = Symbol Digit Modalities Test. Standard deviations in parentheses.

[a] Scores are the sum of clinician-rated items for each scale.

[b] Scores are the total items correct within a given time limit on each scale.

*** $p < .001$.

** $p < .01$.

* $p < .05$.

TABLE 2

Mean results and comparison of RBANS domain and subtest scores at study entry and 16-month follow-up in diagnosed HD patients

RBANS domains and subtests	n	Study entry	Follow-up	t	p	d
Immediate memory	38	71.5 (21.6)	71.4 (20.5)	0.010	.992	0.00
List Learning	38	19.9 (7.8)	19.9 (7.0)	0.000	1.000	0.00
Story Memory	38	11.5 (5.1)	11.3 (4.6)	0.199	.843	0.03
Visuospatial/constructional	36	80.9 (17.1)	81.2 (17.7)	−0.159	.875	−0.02
Figure Copy	36	14.9 (3.2)	13.6 (4.2)	2.169	.037*	0.33
Line Orientation	37	15.3 (3.4)	15.4 (3.5)	−0.221	.826	−0.03
Language	38	83.3 (9.3)	80.0 (12.9)	1.710	.960	0.29
Picture Naming	38	9.7 (0.6)	9.5 (0.8)	1.348	.186 [a]	0.30
Semantic Fluency	38	13.1 (4.0)	12.3 (4.5)	1.215	.232	0.20
Attention	35	66.6 (15.4)	62.5 (14.6)	2.401	.022*	0.28
Digit Span	38	8.2 (2.0)	7.6 (1.9)	2.063	.046*	0.30
Coding	35	25.7 (9.8)	22.6 (10.0)	3.085	.004**	0.31
Delayed memory	35	76.5 (22.0)	73.3 (22.0)	1.080	.288	0.14
List Recall	37	3.4 (3.0)	3.3 (2.7)	0.187	.853	0.02
List Recognition	37	17.8 (2.1)	16.9 (2.7)	2.318	.026* [b]	0.39
Story Recall	37	5.4 (3.2)	5.4 (3.2)	−0.057	.955	−0.01
Figure Recall	35	10.3 (5.0)	8.7 (3.7)	2.444	.020*	0.34
Total scale	34	71.4 (16.8)	68.5 (17.0)	1.845	.074	0.17

Note. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. HD = Huntington disease. Standard deviations in parentheses. Domain and total scores are standard scores ($M = 100$, $SD = 15$). Subtest scores are raw scores.

[a] Wilcoxon Signed Ranks Test, $p = .15$.

[b] Wilcoxon Signed Ranks Test, $p = .046$.

** $p < .01$.

* $p < .05$.