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Neuropsychological manifestations of the genetic mutation for Huntington's disease in presymptomatic individuals

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Abstract

A triplet repeat (*CAG*) expansion mutation in the *huntingtin* gene on chromosome 4 is responsible for Huntington's disease (HD). Presymptomatic genetic testing for this mutation has identified clinically normal persons who are virtually certain to develop this dementing illness if they live a normal lifespan. The present study sought to determine whether these "mutation-positive" persons have impairments in cognitive functioning. Seventy-five mutation-positive persons did not differ from 128 mutation-negative persons on tests selected for their sensitivity to early-stage HD. Interestingly, however, those with the mutation viewed themselves as more likely to develop HD than did those without the mutation. Among mutation-positive subjects, having a longer *CAG* repeat mutation was likewise not associated with cognitive impairment. However, being closer to estimated disease onset (a product of repeat length and parent's age at onset) was associated with selected cognitive impairments. When viewed in light of previous studies showing atrophy of the caudate nucleus and putamen in mutation-carriers who are close to onset but not those far from onset, these results suggest that subtle changes in brain and behavior may be detected shortly before subjects with the HD mutation develop sufficient signs and symptoms for diagnosis. Conceptual and methodological problems associated with the search for presymptomatic cognitive and behavioral indicators of dementing illness are discussed. (*JINS*, 2002, *8*, 918–924.)

Keywords: Huntington's disease, Genetic testing, Striatum, Basal ganglia, Presymptomatic dementia

INTRODUCTION

Genetic testing of asymptomatic people at risk for Huntington's disease (HD) has been available since the late 1980's (Brandt et al., 1989; Hersch et al., 1994). As a result, thousands of neurologically healthy individuals worldwide are known to carry a mutation in the *huntingtin* gene, making their lifetime risk of developing this neurodegenerative disease virtually 100%. The prospective study of these individuals is allowing us to determine the very earliest expression of HD's phenotype, knowledge that is critical for developing and testing preventive interventions.

Brain imaging studies using MRI (Aylward et al., 1994, 1996; Grafton et al., 1990, 1992; Harris et al., 1999), PET (Antonini et al., 1996; Grafton et al., 1990, 1992; Weeks et al., 1996), and SPECT (Harris et al., 1999) have revealed structural and functional changes in the basal ganglia of "mutation-positive" people that precede motor signs of the illness. It is less clear whether any cognitive abnormalities exist prior to clinical onset. Some investigators report that asymptomatic persons with the *huntingtin* mutation perform worse on selected neuropsychological tests than those without the mutation (Foroud et al., 1995; Hahn-Barma et al., 1998; Jason et al., 1997; Kirkwood et al., 2000; Lawrence et al., 1998; Rosenberg et al., 1995). Occasionally, the reported deficits have been extremely highly selective, such as impaired recognition of the facial expression of disgust (Gray et al., 1997). However, other investigators, including ourselves, have found no significant deficits in mutation-positive persons (Blackmore et al., 1995; Campodonico et al., 1996; de Boo et al., 1997, 1999; Rothlind et al., 1993). Differences in subject inclusion criteria, espe-

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cially the care with which patients with motor signs of early-stage disease are screened out, appear to account for many of the discrepancies in results among studies.

Among persons clinically affected with HD, the number of *CAG* repeats in the *huntingtin* gene influences age at symptom onset (Andrew et al., 1993; Stine et al., 1993), correlates positively with striatal atrophy on MRI scans (Rosas et al., 2001), and may influence severity of cognitive impairment or rate of disease progression (Brandt et al., 1996; Illarioshkin et al., 1994; but cf. Kieburtz et al., 1994). In addition, some investigators have reported that *CAG* repeat length is correlated with disease progression or proximity to clinical onset among presymptomatic individuals (Foroud et al., 1995; Hahn-Barma et al., 1998; Jason et al., 1997), making repeat length a potentially significant source of variability among gene carriers.

The present study sought to determine (1) whether any cognitive performance deficits can be observed in a large cohort of neurologically-normal, mutation-positive persons using neuropsychological tests highly sensitive to the presence of HD, and (2) if not, whether there exists a *subset* of mutation-positive persons (i.e., those with long *CAG* mutations or close to clinical onset) who are cognitively impaired.

METHODS

Research Participants

Data were analyzed from all persons at risk for HD (i.e., who had an affected parent) who underwent presymptomatic genetic testing for HD at the Johns Hopkins Hospital between 1987 and 1998. At enrollment into the testing program, each person was administered the Quantified Neurologic Examination (QNE), a standardized assessment of the motor system developed especially for HD (Folstein et al., 1983), as well as a psychiatric examination which included the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978). These assessments were performed by experienced clinicians specializing in HD. Based on the absence of "an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity)" (Huntington Study Group, 1996), each of these at-risk subjects was judged to be clinically unaffected.[1] While the presence of a psychiatric disorder was not used for making the diagnosis of HD, anyone who presented for presymptomatic genetic testing with an active major mental illness was excluded from participation in the research program.

All subjects received extensive education and counseling prior to genetic testing and gave their informed consent before participating (Brandt et al., 1989).

By the end of 1998, 203 persons had received definitive genetic test results: 75 subjects had 37 or more *CAG* repeats (*mutation-positive*) and 128 had 30 repeats or fewer (*mutation-negative*). The mutation-positive and mutation-negative groups differed only in age, with the mutation-positives younger (Table 1). There was a nonsignificant trend toward more minor neurological abnormalities among the mutation-positive cases, but the mean difference was only 1 point and both groups remained well within normal limits.[2]

Procedures

Prior to DNA analysis and disclosure of genetic test results, each participant was administered 10 neuropsychological tests which focused on cognitive and performance domains typically affected early in HD (Brandt, 1991a; Brandt et al., 1989; Campodonico et al., 1996). The battery consisted of the Grooved Pegboard Test (Matthews & Kløve, 1964), Symbol Digit Modalities Test (Smith, 1973), Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981)[3], Standardized Road-Map Test of Directional Sense (Money, 1976), Hopkins Verbal Learning Test (Brandt, 1991b), Trail Making Test (Reitan, 1958), Brief Test of Attention (Schretlen et al., 1996), Stroop Color-Word Test (Golden, 1978; Stroop, 1935), and Wisconsin Card Sorting Test (Heaton, 1981). Fifteen dependent variables were derived from these 10 tests (Table 1).

Each at-risk participant had a partner in the study (typically a spouse, not-at-risk relative or close friend) who participated in some of the pretesting counseling sessions. This person, as well as the at-risk person him/herself, completed a Visual Analogue Scale of Subjective Risk for HD. Each participant drew a vertical mark along a 20-cm horizontal line to indicate how likely it was that the at-risk participant would personally inherit the *huntingtin* gene and therefore become symptomatic. The scale's endpoints were labeled "absolutely certain I (my friend/relative) *will not* develop HD" and "absolutely certain I (my friend/relative) *will* develop HD."

Direct gene testing for the *CAG* expansion in the *huntingtin* gene was performed using polymerase chain reaction by the Genetics Core Facility and the Psychiatric Neurogenetics Laboratory of the Johns Hopkins University School of Medicine. All persons originally tested with linkage markers were retested with the direct gene test when it became available in 1994. Details of the genetic methods can be found in Brandt et al. (1996).

Statistical Analysis

Three sets of statistical analyses were performed. First, the demographic and clinical characteristics and neurocogni-

[1] Although this study began prior to the development of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996), all participants would be rated zero on the 0–4 scale of clinician confidence that a diagnosis of HD is warranted.

[2] The average QNE score of HD patients in our longitudinal core study who were reported by knowledgeable informants to have been clinically symptomatic for 1 year or less was 23.59 (SD = 8.92; n = 17).

[3] The WAIS–R Vocabulary subtest was included as a "hold" measure.

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Table 1. Demographic characteristics and baseline (before DNA testing) clinical characteristics and neuropsychological test results of clinically unaffected persons with and without the *huntingtin* mutation

Participant characteristic	Mutation positive (*CAG* ≥ 37; *n* = 75) *M* (*SD*)	Mutation negative (*CAG* ≤ 30; *n* = 128) *M* (*SD*)	*p*
Baseline characteristic			
CAG repeat length	44.13 (2.48)	21.09 (4.38)	<.001
Age at study entry, years	32.56 (7.61)	36.39 (9.53)	.003
Education, highest grade	15.03 (2.84)	14.46 (2.56)	.239
Quantified Neurological Exam (max. = 123)	3.85 (3.43)	2.99 (2.80)	.053
Test result			
Grooved Pegboard Test			
Dominant hand (s)	63.32 (10.24)	64.38 (10.79)	.621
Nondominant hand (s)	68.61 (13.89)	67.88 (11.07)	.769
Symbol Digit Modalities Test, no. correct	55.65 (9.22)	52.64 (10.24)	.435
Wechsler Adult Intelligence Scale–Revised			
Vocabulary subtest, standard score	10.78 (2.64)	11.45 (2.34)	.241
Block Design subtest, standard score	10.70 (2.71)	10.66 (2.64)	.180
Road-Map Test of Directional Sense (s)	69.00 (24.76)	81.12 (35.67)	.022
Hopkins Verbal Learning Test			
Sum of 3 recall trials (max. = 36)	27.91 (4.74)	28.05 (4.47)	.841
Recognition discrimination (max. = 12)	11.51 (0.85)	11.57 (0.85)	.642
Trail Making Test			
Part A (s)	24.97 (8.80)	27.67 (10.93)	.257
Part B (s)	56.35 (22.76)	63.46 (25.37)	.178
Brief Test of Attention (max. = 20)	17.20 (2.54)	17.09 (3.13)	.667
Stroop Color-Word Test			
Color trial, T score	46.19 (9.36)	45.79 (7.98)	.533
Word trial, T score	46.97 (8.77)	47.73 (8.88)	.322
Color-word trial, T score	49.43 (11.64)	46.22 (10.31)	.336
Wisconsin Card Sorting Test, cards per sort	21.10 (40.07)	17.98 (11.74)	.928

tive test scores of the mutation-positive and mutation-negative groups were compared with MANOVA, followed by a series of independent *t* tests. Due to the large number of univariate comparisons, alpha was set at .01 to minimize both Type-I and Type-II statistical error (Rothman, 1990). Next, the mutation-positive group was split into *shorter-mutation* and *longer-mutation* subgroups using the median *CAG* repeat length of the sample, and these subgroups were compared with *t* tests. Finally, the mutation-positive group was split into *close-to-onset* and *far-from-onset* subgroups, and these subgroups were compared with *t* tests. Proximity to clinical onset of HD was estimated by computing the difference between the person's chronological age and his/her estimated age at onset. Estimated age at onset was calculated based on a regression of eight potential predictor variables on actual age at onset of movement disorder in 82 affected patients (see Campodonico et al. (1996) for more details on the method). Our updated algorithm accounts for 62% of the variance in age at onset using only two variables: *CAG* repeat length in the person whose onset is being predicted and estimated age at onset in his/her affected parent. The prediction equation is estimated age at onset = $56.67 - (0.78 \times$ *CAG* repeat length$) + (0.41 \times$ parental age at onset).

RESULTS

As in our previous reports (Brandt et al., 1989; Campodonico et al., 1996; Rothlind et al., 1993), neuropsychological procedures that are generally sensitive to early HD failed to detect a significant difference between mutation-positive and mutation-negative groups [multivariate $F(15,58) = 0.91$, $p = .56$; see Table 1].[4] On the one neuropsychological test variable where a significant group difference was approached (time to complete the Road-Map Test of Directional Sense), the mutation-positive subjects actually performed better than the mutation-negative subjects.

Mutation-positive subjects rated themselves as somewhat more likely to develop HD than mutation-negative subjects ($p = .04$; Figure 1, left panel). Overall, their partners assigned lower subjective risks, and an even larger difference between positive and negative cases was obtained from their ratings ($p = .008$).

[4] Sample sizes were reduced to 23 mutation-positive and 51 mutation-negative subjects for the MANOVA because of missing data resulting from the later addition of three tests to the protocol.

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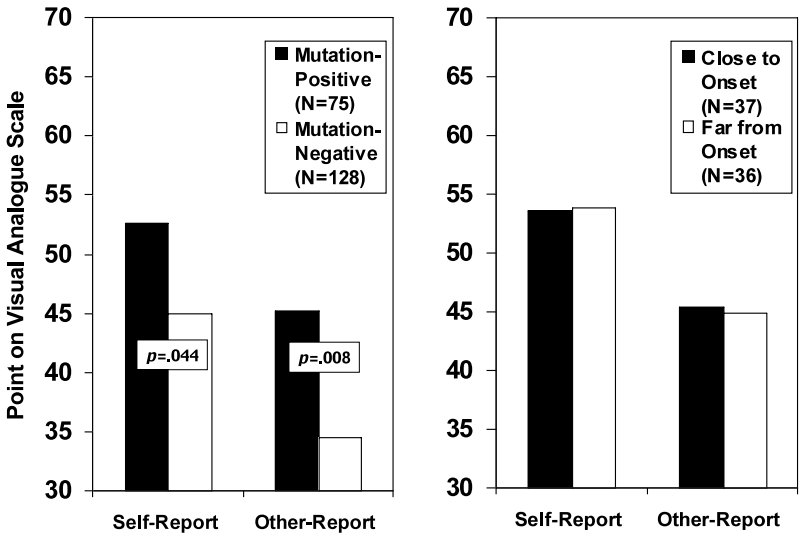

Fig. 1. *Left panel:* Subjective risk of developing Huntington's disease reported by persons undergoing presymptomatic genetic testing (self-report) and their partners (other-report), stratified by genetic test outcome. Score is point on a 20-cm visual analogue scale converted to a percentage or probability (i.e., 50 means as likely to develop HD as not). All testing is prior to DNA analysis and disclosure of test results. *Right panel:* Subjective risk for mutation-positive subjects only, stratified by proximity to clinical onset.

The median *CAG* repeat length among mutation-positive subjects was 44. The shorter-mutation (≤43 repeats) and longer-mutation (≥44 repeats) subgroups did not differ significantly on any of the 15 neuropsychological test variables, although the longer-mutation subgroup was slightly younger ($M = 30.63$ years *vs*. 34.77 years; $p = .02$) and had slightly higher scores on the neurological exam ($M = 4.60$ points *vs*. 3.00 points; $p = .04$).

Proximity to onset could not be calculated for two mutation-positive subjects, as reliable estimates of age at onset in their affected parents were not available. The median proximity to onset for the remaining 73 mutation-positive subjects was 8.11 years. The sample was split at this value into close-to-onset and far-from-onset subgroups. Although both subgroups had QNE scores well within the clinically normal range, they did differ in mean score (Table 2). Importantly, statistically significant differences ($p < .01$) were found on 6 of the 15 neuropsychological variables. The close-to-onset group was more severely impaired on the Symbol Digit Modalities Test, WAIS–R Block Design subtest, Road-Map Test of Directional Sense, and Stroop Color-Word Test (all three trials). These tasks require spatial analysis, constructional praxis, response inhibition, and rapid response execution. Purely auditory–verbal tasks, such as the WAIS–R Vocabulary subtest, Hopkins Verbal Memory Test, and Brief Test of Attention, were not significantly different between close-to-onset and far-from-onset subgroups. Because the subgroups differed in the number of minor motor signs, the data were reanalyzed with analysis of covariance, removing the variance shared with QNE scores. The subgroups remained significantly different ($p < .01$) on the Symbol Digit Modalities Test, Road-Map Test of Directional Sense, and all three trials of the Stroop Color-Word Test. When age was included as a second covariate, the differences between groups were reduced to a trend ($p < .05$) on the Road-Map Test of Directional Sense and the color trial of the Stroop Color-Word Test.[5]

In spite of the fact that close-to-onset subjects had selective performance deficits, they did not report a higher subjective risk of developing HD than did their far-from-onset peers (Figure 1, right panel). The partners of close-to-onset and far-from-onset subjects also gave similar judgments.

DISCUSSION

Like previous studies from our Center, the present study found that clinically healthy people with the *CAG* expansion in *huntingtin* were, as a group, unimpaired on cognitive tests that are sensitive to the presence of HD. While several other research groups have reported otherwise, many of their studies have had serious methodologic flaws. Paramount among these has been the inclusion of people already mildly symptomatic with HD in their mutation-positive groups. For example, Foroud et al. (1995) included in their study of HD gene carriers all at-risk people who *reported themselves to be* free of symptoms. These 120 people were found to perform worse than 260 noncarriers on two of the six WAIS–R subtests administered (Picture Arrangement and Digit Symbol). However, when the analyses were limited to the 48 gene carriers who were

[5]Covarying the effect of age in a comparison of close-to-onset and far-from-onset groups runs the risk of removing variance associated with the independent variable. This analysis was performed, and the results reported, for the sake of completeness.

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Table 2. Influence of proximity to onset on cognitive functioning in clinically unaffected persons with the *huntingtin* mutation

	Close to onset (≤8.11 years; $n = 37$)	Far from onset (≥8.12 years; $n = 36$)	
Participant characterisitc	*M* (*SD*)	*M* (*SD*)	*p*
Baseline characteristic			
CAG repeat length	44.86 (2.51)	43.53 (2.26)	.019
Age at study entry, years	35.32 (6.02)	28.67 (5.22)	<.001
Education, highest grade	15.51 (2.80)	14.47 (2.73)	.112
Quantified Neurological Exam (max. = 123)	5.03 (4.03)	2.75 (2.25)	.004
Proximity to onset, years	3.97 (3.49)	13.07 (3.74)	<.001
Test result			
Grooved Pegboard Test			
Dominant hand (s)	65.29 (8.15)	60.50 (10.45)	.134
Nondominant hand (s)	72.94 (16.52)	63.25 (6.35)	.034
Symbol Digit Modalities Test, no. correct	52.62 (9.53)	59.58 (8.51)	.002
Wechsler Adult Intelligence Scale–Revised			
Vocabulary subtest, standard score	10.76 (2.39)	10.42 (2.32)	.567
Block Design subtest, standard score	10.61 (2.52)	12.45 (2.67)	.005
Road-Map Test of Directional Sense (s)	78.09 (23.88)	58.12 (21.70)	.002
Hopkins Verbal Learning Test			
Sum of 3 recall trials (max. = 36)	27.03 (5.17)	28.55 (4.18)	.202
Recognition discrimination (max. = 12)	11.39 (0.99)	11.61 (0.70)	.309
Trail Making Test			
Part A (s)	28.21 (11.01)	23.19 (6.66)	.096
Part B (s)	65.47 (25.59)	49.57 (15.55)	.026
Brief Test of Attention (max. = 20)	16.32 (2.47)	17.25 (2.15)	.215
Stroop Color-Word Test			
Color trial, T score	42.03 (8.38)	48.97 (7.67)	.001
Word trial, T score	43.29 (7.25)	49.33 (7.80)	.002
Color-Word trial, T score	44.97 (8.99)	52.42 (8.80)	.001
Wisconsin Card Sorting Test, cards per sort	27.61 (45.95)	13.66 (3.03)	.087

Note. The Trail Making Test and the Brief Test of Attention were added to the protocol midway into the study. The sample sizes for these tests are reduced to 18 close-to-onset and 22 far-from-onset subjects.

normal on neurologic examination, there were no significant differences. Since as many as 34% of those with the *huntingtin* mutation who describe themselves as asymptomatic have either manifest HD or "major soft signs" (e.g., possible chorea; Siemers, Foroud, Bill et al., 1996), studies that do not include careful examination of participants and the exclusion of those who are already probably affected can hardly be said to be studies of presymptomatic gene-carriers.

While the mutation-positive subjects in this study, as a group, were cognitively unimpaired, they judged themselves, and their partners judged them, as more likely to develop HD than those without the mutation. This is particularly noteworthy as the subjective risk scale, like the neuropsychological testing, was completed prior to DNA analysis. It may suggest that our cognitive tests are not detecting characteristics of mutation-positive people that they, and those close to them, observe in themselves. What these characteristics are (e.g., extremely subtle cognitive inefficiencies or mood alterations, decreased fluidity of movements) remains for future studies to determine.

In and of itself, having a short or long *CAG* expansion in the *huntingtin* gene did not predict cognitive impairment. However, estimated proximity to HD symptom onset, which depends on *CAG* repeat length, did. People in the close-to-onset subgroup, who were, on average, 4 years prior to predicted onset, had mild, selective cognitive impairments. These were largely in the realms of spatial cognition and processing speed. Although the close-to-onset subjects were, on average, 6.7 years younger than the far-from-onset subjects, they were not at an age where significant aging-related deficits are expected. Our finding, coupled with the fact that striatal atrophy on MRI scans is seen only in people judged to be within 6 years of onset (Aylward et al., 1996; Campodonico et al., 1998; Harris et al., 1999), suggests that cognitive deficits are observed only when the basal ganglia have degenerated to some critical level.

Given the critique of previous studies levied above, it might be argued that the presence of cognitive impairment and very subtle findings on the Quantified Neurological Exam in our close-to-onset subjects means that they are actually showing signs of illness and should therefore be considered "affect-

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ed" rather than "presymptomatic." In some ways, this is more a question of semantics or philosophy than science (i.e., is the presence of signs or symptoms in presymptomatic individuals an oxymoron?). Nonetheless, two facts argue against this interpretation. First, the motor abnormalities in our close-to-onset subjects are so subtle as to be unnoticeable to casual observation and grossly insufficient for diagnosis of HD even by clinicians specializing in the illness (and who might, therefore, have a lower-than-average threshold for diagnosis). Second, the cognitive impairments of these subjects persisted when the effects of their negligible motor signs are removed by analysis of covariance.

It is interesting to note that although the mutation-positive subjects perceived themselves to be at higher risk of developing HD than the mutation-negative subjects (and their partners concurred), those who are nearing onset did not have a higher subjective risk than those far from onset. This may, in part, reflect the older age of the close-to-onset subgroup. At least some of these subjects may consider themselves "escapees" because they remain unaffected at ages near those at which their affected parents became ill.

It might be most fruitful for future studies of the behavioral/cognitive phenotype of those with the HD mutation to focus on aspects of motor control, spatial cognition, and skill acquisition that are difficult to assess with off-the-shelf clinical neuropsychological tests. Recent laboratory-based studies using testing paradigms that allow a fine-grained analysis of psychomotor performance have revealed significant defects in controlled arm movements and pattern learning in some presymptomatic mutation carriers (Ghilardi et al., 2001; Smith et al., 2000). The combination of such behavioral studies with functional imaging of the neostriatum and related structures believed to be involved in motor programming, sequencing, timing, and/or on-line error correction (Feigin et al., 2001; Grafton, 1995; Harrington et al., 1998; Lawrence, 2000; Smith & Shadmehr, 2000) may help reveal the very earliest phenotypic expression of the *huntingtin* mutation.

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