

SHORT REPORT

Neuropsychological stability over two years in asymptomatic carriers of the Huntington's disease mutation

Jeffrey R Campodonico, Ann Marie Codori, Jason Brandt

Abstract

This study examined whether neuropsychological changes emerge over time in asymptomatic adults who have the Huntington's disease mutation. We also evaluated whether scores on cognitive tests or psychological symptom scales varied as a function of CAG repeat length or proximity to disease onset. Twenty two healthy "mutation positive" and 37 "mutation negative" adults completed cognitive tests and psychological rating scales before disclosure of their genetic test results and on an annual basis thereafter. Repeated measures ANOVAs analysed differences between the two groups over three assessments. Correlations of cognitive and psychological symptom test scores with estimated number of years to disease onset and CAG repeat length were computed. The two groups did not differ at study entry; nor did they differ in the rate of change over time. Tests of sustained attention and mental speed correlated with estimated years to disease onset, but not with repeat length. As a group, clinically asymptomatic adults with the Huntington's disease mutation do not display neuropsychological deficits when studied over a two year interval. However, persons who are likely nearing clinical onset of Huntington's disease may develop minor deficits in selected cognitive domains before they reach threshold for diagnosis.

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With the discovery that an expanded trinucleotide repeat (CAG) in the IT-15 gene on chromosome 4 constitutes the mutation for Huntington's disease,¹ it has become possible to examine whether presymptomatic neuropsychological changes occur in persons destined to become ill. Most studies of persons at high risk ($\geq 95\%$) and low risk ($\leq 5\%$) based on DNA linkage analysis² found no differences in cognitive performance or emotional functioning.³⁻⁶ The few studies that reported group

differences⁷⁻⁹ had significant methodological shortcomings.³

We examined neuropsychological performance prospectively in a relatively large group of persons who were tested for the Huntington's disease mutation and who were judged to be asymptomatic based on a standardised, quantified neurological examination¹⁰ and psychiatric interview.¹¹ Our supposition was that studying these subjects for two years would disclose whether gene carriers decline in cognitive or emotional functioning at a time when they are unambiguously free of chorea or other clinically significant symptoms of Huntington's disease. We also examined whether any such changes are more likely to appear in gene carriers nearer their estimated time of onset of disease. Finally, as the Huntington's disease mutation is a DNA fragment expansion of varying length, we examined the relation between number of CAG repeats and neuropsychological test performance.

Method

SUBJECTS

Twenty six adults at risk for Huntington's disease (by virtue of having an affected parent) who tested positive for the Huntington's disease mutation ("mutation positive") and 37 adults who tested negative ("mutation negative") were studied. All subjects were participants in the presymptomatic testing programme of the Baltimore Huntington's disease project at the Johns Hopkins University School of Medicine. A detailed review of the entry criteria and testing protocol has appeared elsewhere.¹²

For this study, subjects were included only if they completed a baseline assessment, received disclosure of their genetic test results, and completed one year and two year postdisclosure follow up assessments as of January 1995. All subjects were required to remain free of any movement disorder or emotional or behavioural disturbance indicating clinical onset of Huntington's disease for the two year period. Four subjects were diagnosed with Huntington's disease before their two year follow up visit and are excluded from the analysis described here. The remaining 22 mutation positive subjects met all the above criteria and constitute the subjects of interest.

Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, USA

J R Campodonico
A M Codori
J Brandt

Correspondence to:
Dr Jason Brandt,
Department of Psychiatry
and Behavioral Sciences,
Meyer 218, The Johns
Hopkins Hospital, 600 North
Wolfe Street, Baltimore,
Maryland 21287-7218,
USA.

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NEUROPSYCHOLOGICAL TESTS

A battery of cognitive tests and psychological symptom rating scales were completed by subjects before DNA analysis and at annual re-evaluations. Neuropsychological tests were selected based on their established sensitivity to the impairments in Huntington's disease.¹³ The tests included the Wechsler adult intelligence scale-revised (WAIS-R) (vocabulary and block design subtests)¹⁴; standardised road map test of directional sense¹⁵; extrapersonal orientation test^{16,17}; Hopkins verbal learning test (HVL)^{18,19}; symbol digit modalities test²⁰; Stroop colour and word test²¹; Wisconsin card sorting test²²; cognitive failures questionnaire²³; Beck depression inventory (BDI)²⁴; Beck Hopelessness scale²⁵; and symptom checklist-90-revised (SCL-90-R).²⁶ In addition to these neuropsychological measures, the quantified neurological examination (QNE)¹⁰ was completed by a neuropsychiatrist or research nurse at each visit.

CALCULATING ESTIMATED NUMBER OF YEARS TO DISEASE ONSET

The number of years to disease onset was estimated for each mutation positive subject. Previous research disclosed that the *CAG* repeat length of an at risk person, age at onset of the affected parent, and sex of the affected parent are each predictive of the age at onset in the at risk person.²⁷ These three variables from a sample of 50 patients from the Huntington's disease clinic were entered into a stepwise multiple regression analysis to predict age at onset. Parental age at onset entered the equation first ($F(1,48) = 44.3$, $\beta = 0.53$, $P < 0.0001$), followed by *CAG* repeat length ($F(2,47) = 40.4$, $\beta = -0.42$, $P < 0.0001$). Sex of the affected parent did not pass the tolerance test ($P_{in} = 0.05$). The resulting prediction formula (estimated age at onset = $(-0.81 \times \text{repeat length}) + (0.51 \times \text{parental onset age}) + 54.87$) accounted for 64% of the variance in subjects' ages at onset. Cross validation of the regression equation in a new sample of 115 patients with Huntington's disease from our Huntington's disease clinic supported the predictive accuracy of the equation in estimating disease onset ($R^2 = 0.50$, $P < 0.0001$). Based on this formula, a "years to onset" score was computed for each subject by subtracting his or her age at study entry from his or her estimated age at onset of Huntington's disease.

Table 1 Demographic and baseline clinical information for subject group

	Mutation positive (n = 22)	Mutation negative (n = 37)	P value
Male/female	9/13	14/23	
Age (y)	31.9 (6.1)	35.8 (8.9)	0.07
Education (y)	14.7 (2.7)	14.4 (2.7)	0.60
% Right handed	86	84	
Sex of affected parent, M/F	9/13	14/23	
Age of onset of affected parent (y)	42.9 (9.8)	40.7 (13.1)	0.52
<i>CAG</i> repeat length	44.4 (2.2) range 41-51	22.4 (3.3) range 16-35*	0.0001
Estimated years to onset	9.0 (4.0) range = 1.7-16.4	—	
Quantified neurological examination (max = 123)	2.9 (3.2) range 0-11	1.7 (2.1) range 0-7	0.11

Results are means (SD).

*One mutation negative subject had a repeat length of 35, which was determined to have been inherited from the unaffected grandparent. The next longest repeat length was 25.

DATA ANALYSES

Mutation positive and mutation negative groups were compared on baseline psychological symptoms and test performances using one tailed *t* tests. As type II statistical errors (failure to detect real group differences) were considered less desirable than type I errors, α level (0.05) was not corrected for multiple comparisons. Repeated measures analyses of variance (ANOVAs) were used to analyse differences between the two groups across the three examination sessions. Group status (mutation positive and mutation negative) was the between subjects factor and visit (baseline, one year, and two year follow up) was the repeated measures factor.

Pearson product moment correlations (one tailed) between *CAG* repeat length and change in test scores over the two year study were computed for mutation positive subjects. The change in test performance was calculated for each neuropsychological variable by subtracting the score obtained on the two year follow up visit from that obtained at baseline. Higher change scores reflect either an improvement or decline (depending on the test used) in test performance over time. Pearson correlations between the estimated number of years to onset and the change in neuropsychological test scores were also computed.

Results

Table 1 presents the demographic and baseline clinical characteristics of the two groups. The mutation negative participants were slightly older than the mutation positive patients, although the difference only approached significance. This trend is consistent with previous reports and reflects the high probability that older gene carriers would already be symptomatic and thus excluded from the study. There was no significant difference in QNE score between the two groups, with all subjects scoring well within normal limits. (At the time of diagnosis, recent onset patients typically obtain scores above 15.)

BASELINE COMPARISONS

Mutation positive and mutation negative groups did not differ on any of the baseline cognitive tests or psychological symptom scales, including the tests typically performed abnormally very early in Huntington's disease.²⁸ The findings were unaffected by covarying for age.

LONGITUDINAL ANALYSES

There was a significant main effect of Group only on the QNE and on the hostility subtest of the SCL-90-R (table 2). Mutation positive subjects had higher QNE scores overall and reported greater interpersonal anger than mutation negative participants across visits. The effect of visit was significant for many cognitive and psychological symptom measures, with both groups performing better cognitively and reporting fewer psychological symptoms across visits. These findings likely reflect a combination of practice effects and resolution

Table 2 Longitudinal comparisons between mutation positive and mutation negative groups on cognitive tests and psychological symptom scales

Test	Mutation positive				Mutation negative			P value		
	No	Baseline	1y	2y	Baseline	1y	2y	Group	Visit	G × V
QNE (total)	55	3.2	3.7	2.2	1.8	1.8	2.2	0.01	0.17	0.63
Cognitive tests:										
WAIS-R:										
Vocabulary	59	10.0	10.4	10.2	10.6	10.6	11.0	0.39	0.26	0.29
Block design	59	10.9	11.5	12.0	11.1	11.4	11.9	0.96	0.01	0.68
Estimated IQ	59	103.7	106.8	107.2	105.8	107.6	109.6	0.57	0.01	0.65
Wisconsin card sorting test:										
Inefficiency ratio	59	25.4	13.6	13.0	20.2	16.7	14.5	0.94	0.01	0.37
Perseverative errors	59	3.9	1.0	0.7	3.9	1.6	1.2	0.61	0.01	0.88
Symbol digit modalities test:										
Oral	52	67.0	73.5	74.5	63.5	70.8	72.5	0.57	0.01	0.83
Written	52	56.2	65.2	66.1	54.2	62.6	63.7	0.53	0.01	0.96
Stroop test:										
Colour	57	45.2	46.6	45.6	46.8	48.3	48.1	0.34	0.30	0.85
Word	57	45.0	44.2	43.8	46.6	47.3	48.1	0.17	0.98	0.38
Colour/word	57	48.6	46.8	48.4	47.9	49.1	49.3	0.72	0.64	0.29
Interference	57	50.8	52.8	51.2	51.4	49.6	50.7	0.56	0.98	0.35
Standardised road map test:										
Time(s)	53	80.6	81.7	77.3	80.2	82.1	68.5	0.79	0.13	0.56
Errors	53	2.8	1.3	2.3	3.2	1.5	2.3	0.73	0.01	0.88
Hopkins verbal learning test:										
Recall (total)	59	27.2	28.1	28.0	27.8	28.7	28.8	0.61	0.61	0.81
Discriminability index	59	11.2	11.3	11.5	11.6	11.7	11.3	0.38	0.86	0.39
Extrapsessional orientation test:										
No turn condition										
Time(s)	55	15.5	14.6	14.7	17.9	15.1	13.9	0.58	0.01	0.07
Errors	55	0.4	0.2	0.2	0.8	0.4	0.2	0.37	0.06	0.50
Turn condition										
Time(s)	55	27.9	28.2	25.9	30.3	26.3	24.8	0.96	0.01	0.19
Errors	55	2.1	2.6	1.6	2.2	1.8	1.7	0.84	0.36	0.37
Cognitive failures										
Questionnaire	48	30.4	26.1	27.4	29.7	28.2	31.2	0.59	0.09	0.26
Psychological symptom scales:										
Beck depression scale	56	3.4	1.4	2.1	1.8	1.5	2.5	0.53	0.01	0.45
Beck hopelessness scale	54	3.2	3.0	2.8	2.6	1.8	2.2	0.24	0.19	0.56
SCL-90-R:										
Somatisation	55	49.8	43.8	48.4	45.9	43.7	45.1	0.24	0.01	0.31
Obsessive-compulsive	55	53.4	45.3	49.7	48.8	47.1	47.4	0.56	0.01	0.14
Interpersonal sensitivity	55	55.2	46.6	48.9	51.8	44.5	49.5	0.43	0.01	0.40
Depression	55	51.2	45.3	44.5	49.8	46.0	46.7	0.83	0.01	0.56
Anxiety	55	51.1	45.2	47.2	48.3	43.0	45.7	0.33	0.01	0.92
Hostility	55	52.5	44.1	48.4	47.6	41.3	44.6	0.03	0.01	0.87
Phobic anxiety	55	46.1	44.1	45.2	42.9	42.6	45.3	0.31	0.38	0.48
Paranoid ideation	55	50.1	41.7	43.2	47.1	42.3	44.6	0.85	0.01	0.27
Psychoticism	55	52.2	46.1	46.2	48.6	45.9	46.7	0.50	0.01	0.38
Positive symptom										
Distress index	55	52.1	46.9	50.4	47.8	44.4	45.4	0.06	0.02	0.69
Positive symptom										
Total	55	52.6	45.1	43.4	47.3	43.1	45.4	0.47	0.01	0.07
Global severity index	55	52.6	45.2	46.5	48.8	44.1	46.1	0.40	0.01	0.36

The analysis excluded subjects with missing data. Thus sample sizes may be different from baseline analysis due to the requirement that subjects have three visits. Standard scores were calculated for WAIS-R, Stroop, and SCL-90-R variables based on published norms. Raw scores were reported for all other tests. All of the tests are commercially available in the USA.

WAIS-R estimated IQ score was based on the mean of the combined vocabulary and block design subtests.

Wisconsin card sorting test "inefficiency ratio" denotes cards/sorts (higher scores reflect greater inefficiency).

of the uncertainty associated with the baseline period. Most importantly, none of the group × visit interactions reached significance. None of these findings was altered by covarying for age. Thus mutation positive and mutation negative groups did not vary in their rate of change over time.

CORRELATIONS WITH CAG REPEAT LENGTH

A single significant correlation with repeat length was found. Greater change in performance of the extrapsessional orientation test (a route finding test in which subjects must transverse a pattern of positions on the floor according to a map held in their hands) correlated with longer repeat length ($r = 0.38$, $P < 0.05$). However, the result was in the unexpected direction, as higher change scores for this test reflect improvement.

CORRELATIONS WITH ESTIMATED YEARS TO ONSET

Years to onset score correlated with change on the symbol digit modalities test (written) ($r = -0.55$, $P < 0.005$) and the Stroop test (colour subtest) ($r = -0.53$, $P < 0.01$). Subjects who at baseline were closer to their estimated onset

showed greater declines in attention and mental speed over the subsequent two years. No other correlations were significant.

Discussion

If neuropsychological changes precede the onset of involuntary movements in Huntington's disease and develop in an insidious and gradual manner, persons testing positive for the Huntington's disease mutation might be expected to show subtle yet measurable changes in cognitive and emotional functioning over time. However, our study did not detect any significant differences between mutation positive and mutation negative groups over a two year testing period, even using very sensitive neuropsychological tests and liberal statistical criteria. Although contrary to some findings,⁷⁻⁹ our results are consistent with others.³⁻⁶

Our results are consistent with the recent longitudinal study of Giordani *et al.*,⁶ who found no differences in neuropsychological performance between DNA marker positive and marker negative groups. The fact that our study also found no differences, using a larger

sample and the direct test for the Huntington's disease genetic mutation rather than linkage testing, supports these earlier findings. In addition, we did not find any associations between repeat length and scores on the cognitive tests or psychological symptom scales in Huntington's disease gene carriers, suggesting that persons with longer repeats are at no greater risk for developing minor neuropsychological deficits before onset of disease than those with shorter repeats. However, it is important to note the restricted range of CAG repeats (41–51) in our sample.

Whereas the present findings argue against preclinical neuropsychological changes in asymptomatic gene carriers, our conclusions may be limited in two important respects. Firstly, our analysis was limited to two years of follow up. It is possible that group differences might be detected as subjects are followed up for longer. Secondly, it could be argued that neuropsychological deficits emerge shortly before onset of chorea. If this is true, it may be too early to detect any changes in our sample, as our mutation positive subjects were, on average, 9 years younger than the age at which they are most likely to become ill.

We examined associations between subjects' change in test performance over the two year study and their estimated "years to onset" based on an empirically derived formula. Although most of the correlations failed to reach significance, subjects closer to estimated onset at baseline performed worse on tests of sustained attention and mental processing speed over time than those further away from onset. It may be that these cognitive declines signal the earliest brain changes of Huntington's disease. This interpretation is supported by recent MRI and PET studies showing smaller basal ganglia volume and lower caudate glucose metabolism in healthy presymptomatic persons.^{29–31} In fact, preliminary data from our Huntington's disease centre suggest that the striatum atrophies as patients approach their estimated onset of movement disorder.³² We are currently determining whether MRI volumes of the basal ganglia disclose significant associations between regional brain size and cognitive deficits in asymptomatic subjects. Whereas it is possible that cognitive declines in gene carriers result from the emotional distress of learning the genetic test results, the absence of any correlations between "years to onset" and scores on the psychological symptom scales does not support this interpretation. Continued study of this sample, and the inclusion of other tested people who meet the follow up criteria, will help establish more definitively the sequence of events that unfold early in Huntington's disease.

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