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Cognitive performance in UK sample of presymptomatic people carrying the gene for Huntington's disease

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Abstract

This paper presents an investigation of cognitive ability in 30 subjects at risk for Huntington's disease. Those shown to be at high or low risk for this disease are compared on a wide range of neuropsychological measures. Results indicate only one significant difference between the two groups; those who carry the gene show a higher level of performance on the Corsi Supraspan task. It is suggested, however, that minimal deficits are apparent in the at risk gene carrying group but that current measures of assessment are not sensitive enough to identify them.

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Huntington's disease (HD), described by George Huntington in 1872, is an autosomal dominant neurodegenerative disorder. People with the disease typically present with a choreic movement disorder, personality changes, and a progressive dementia. The age of onset is usually in the fourth or fifth decade, and most patients have offspring by the time the diagnosis is made. These people are at 50% risk of developing HD. There is evidence that there is a prodromal phase in HD where subtle but detectable behaviour and mnestic difficulties can be detected. Wilson and Garron[1] argue that it is possible to show this phase even in pre-adolescence. Research into this area was thought to be of practical use since if evidence for a prodromal phase was found then it could be used as a presymptomatic predictive test. In 1983, Gusella *et al*[2] found DNA probes linked to the Huntington's locus on chromosome 4 which allowed predictive testing for some families. These tests usually had an accuracy of 95% or greater. More recently the mutation for this disease has been characterised (Huntington's Disease Collaborative Research Group, 1993[3]) which offers accurate testing for at risk subjects. The possibility of a prodromal phase is nevertheless of great scientific interest since it may provide improved knowledge of how and at what stage the gene for Huntington's disease begins to manifest itself, and thus could provide further evidence of the mode of action of the mutated gene.

Evidence for a prodromal phase in Huntington's disease has focused on psychometric tests. This is perhaps not surprising since several studies indicate that intellectual deterioration is evident early on in the Huntington's disease process. Butters *et al*,[4] for example, note that within one year of diagnosis deficits were detectable in the Digit Symbol and Picture Arrangement subtests of the Wechsler Adult Intelligence Scale (WAIS) and in the Logical Memory and Associate Learning subtests of the Wechsler Memory Scale (WMS). There are clear indications of cognitive decline shortly after diagnosis but the main question in the present context is whether or not these deficits can be detected in those people who carry the gene but who have no classical clinical features of the disease.

Until recent developments in the use of recombinant DNA technology for presymptomatic testing, research into this prodromal phase was restricted to two methodologies. Longitudinal studies were based on administering cognitive tests to at risk subjects and then comparing the results of those who go on to develop Huntington's disease some time later with those who remain symptom free. Using this approach support for the association between cognitive test results and the HD gene became more apparent in the 1970s following publications by Lyle and Quast[5] and Lyle and Gottesman.[6 7] These papers reported a follow up study of 88 at risk subjects, originally assessed by Pearson *et al*,[8] as part of the Minnesota Kinship study. Even though assessments took place long before any subjects showed obvious signs of HD, examinations of their results indicated that those 28 at risk subjects who had in fact gone on to develop the disorder showed markedly lower results on the Shipley, Bender Gestalt Recall, and Wechsler Adult Intelligence tests, than did those 60 at risk subjects who did not. This difference was still significant considering only those at risk subjects who had gone on to develop HD six to eight years after original testing. It was also apparent that IQs of those who went on to develop HD averaged 15 points less (1 SD) than did the IQs of those who did not.

These findings were encouraging, supporting the view that psychometric tests could lead to a means of detecting possible deficits in the at risk population. Longitudinal studies, however, do have limitations. There is always a danger that subjects will drop out of such studies or be untraceable at the time of follow up. In the Lyle *et al*[5-7] studies, 50% of the original sample could not be used in final analysis. Additionally there is always a risk that Huntington's disease could still develop in those at risk subjects classified at follow up as being symptom free, because of the variability of age of onset.

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Test performance of samples of the at risk population as a whole have been compared with normal controls,[9-11] using a method which avoids the pitfalls of longitudinal study. Fedio *et al*,[9] for example, reported at risk subjects to be significantly impaired on a number of measures, including the Digit Span subtest of the WAIS, Money's Road Map of Directional Sense, and the Stylus Maze Task. Overall studies suggest that deficits in the at risk population are most detectable in the areas of memory, in particular memory recall, in visuospatial abilities, and in tasks sensitive to frontal lobe dysfunction. Results are encouraging but these comparative studies also have a number of problems.

In any sample of the at risk population slightly fewer than half will be gene carriers (since a proportion will have already developed the condition). If differences do exist between those at risk subjects who have the HD gene and normal control subjects, then these differences may be obscured by combining their data with those at risk subjects who do not have the gene. It is also questionable as to whether or not it is valid to compare at risk subjects with normal controls at all. At risk groups as a whole are subject to a different kind of stress not experienced by normal control groups and there is evidence to support the fact that stress can impair cognitive ability.[12] Very often at risk subjects have the added stress of a parent or grandparent already affected by Huntington's disease. They may also be nervous in the test situation if they believe that the results of cognitive assessments could give an indication as to whether or not they will develop the disorder or confirm fears that they already have the disease.

Since the advent of the presymptomatic test based on DNA analysis an improved research design has been possible. Those at risk people most likely to develop the condition can be compared directly with those least likely to. Comparing at risk groups with each other avoids at least some of the difficulties encountered when comparing at risk subjects with normal controls. First to take advantage of this new research methodology were Jason *et al.*[13] The DNA marker used in their study was approximately 95 to 96% accurate. The researchers, therefore, could be 95% confident that those in the high risk group (AR+) did carry the gene while those in the low risk group (AR−) did not. Comparing performance of these two groups on a large battery of cognitive measures Jason *et al*[13] found that those in the AR+ group had poorer performances on the WMS Visual Recall Test ($p<0.02$), the Wisconsin Card Sorting Test ($p<0.02$), the Warrington Dot Discrimination Task ($p<0.02$), and the two point discrimination threshold for the right palm ($p<0.03$). Overall deficits in the AR+ group were most apparent in the area of visual spatial abilities and in some skills usually associated with cortical lesions to the frontal lobes. General intelligence, motor performance, verbal memory, and language abilities appeared unaffected.

The work of Jason *et al*[13] looks promising. However, their conclusions have been carefully scrutinised by Strauss and Brandt[14] who found that it is premature to conclude that the cognitive differences between the two groups correspond to the presence or absence of the Huntington's gene. Sample sizes in the study were very small, only seven in the AR+ group and three in the AR− group. Additionally, all subjects came from only three pedigrees. Differences in cognition could have arisen from genetic influences unrelated to the HD gene. Jason *et al*[13] also failed to include statistical controls for type 1 errors when analysing their results. Strauss and Brandt[14] reported new data obtained from a larger pool of subjects, 12 AR+, 15 AR−, and 15 normal controls included in final analysis. A wide ranging neuropsychological test battery was used but this failed to confirm any of the findings of Jason *et al.*[13] None of the differences between AR+ and AR− groups was significant, even at the 0·05 level.

The findings of Strauss and Brandt[14] are disappointing to those who support the presence of a prodromal phase. However, a more recent study by Diamond *et al*[15] presents a slightly different analysis and resulting conclusion. In the study of Diamond *et al*,[15] 10 AR+ and eight AR− subjects were compared on a large battery of tests measuring cognitive ability, including the WAIS-R, WMS, Wisconsin Card Sorting Test, and Trail Making tests. Excluding tests at which subjects performed at ceiling, results of the remaining 19 measures are interpreted in terms of "advantage", with the AR− group being advantaged (that is, with a higher mean performance) on 16 of the tests and the AR+ group being advantaged on only three. Statistical analysis, however, reports only one significant difference, at the 5% level, between these two groups; AR− subjects performed significantly better on the Paired Associate Learning subtest of the Wechsler Memory Scale. On no other measures of cognitive ability did differences in mean performance reach significance.

Clearly the results of the three studies based on the improved methodology using results based on DNA analysis leave us somewhat sceptical of the presence of a prodromal phase in Huntington's disease, although the references of Diamond *et al*[15] to "advantage" suggest it still may be a possibility. The need for further research in this area is evident. To improve validity and power of statistical tests sample sizes must be improved. It is also noticeable that previous studies have entirely depended upon North American samples. The present study investigates cognitive performance of AR+ and AR− subjects on a wide range of cognitive measures. Subjects are taken from a sample within the UK.

Methods

SUBJECTS

All subjects used in the present study were referred by Dr Sheila A Simpson (Department of Medical Genetics, Aberdeen Royal Infirmary

NHS Trust). The 30 subjects were derived from a larger group of people all of whom had sought a presymptomatic test for Huntington's disease. Subjects were excluded from the study if psychiatric or neurological assessments suggested that they were already affected, or if after counselling they decided they did not wish a result. In each case the presence of Huntington's disease in their family and a suitable family structure for the purpose of DNA testing was confirmed. After cognitive testing had taken place, data from this initial group of 30 was subdivided, for the purpose of analysis, into two further groups, determined by the presence or absence of the Huntington's disease gene, as shown with 98 to 99% accuracy by linkage analysis. This yielded an AR+ group of 13 and an AR− group of 17. The mean age and years of education for the AR+ group were 31·9 (SD 10·3) and 11·7 (SD 2·0) respectively. For the AR− group corresponding figures were 38·5 (SD 11·4) and 11·6 (SD 2·2). Neither of these differences were significant.

All subjects who took part in the study volunteered to do so and all received a small remuneration towards the cost of any expenses incurred. The study obtained the Joint Ethical Committee approval from Grampian Health Board.

PROCEDURE

The neuropsychological test battery administered consisted of a total of 17 tasks, which were divided into three sessions as follows.

Session 1

Wechsler Adult Intelligence Test – Revised.[16 17]
National Adult Reading Test.[18]

Session 2

California Verbal Learning Test (CVLT).[19]
Corsi Blocks.
Corsi Block Supraspan.[20]
Digit Supraspan.
Cognitive Estimation Task.[21]
Wisconsin Card Sorting Test – Modified (WCST).[22]
Verbal Fluency.[23]
Purdue Peg Board.[24]

Session 3

Pursuit Rotor.[25]
Benton Visual Retention Test.[26]
Reitan Trails A and B.[27]
Finger Tapping.[28]
Word Completion Task 1 and 2.[29]
Judgement of Line Orientation.[30]
Paced Auditory Serial Addition Task (PASAT).[31]

Items were selected for the test battery because of their known sensitivity to Huntington's disease in affected samples.[32] Test sessions were restricted to a maximum of one and a half hours in length. It was thought to be inadvisable to make test sessions any longer since subject fatigue could influence performance in tasks later in the session. For all measures standard procedures of administration and scoring were adhered to.

Genetic linkage analyses for the Huntington's disease gene locus were carried out at the Department of Medical Genetics, Aberdeen Royal Infirmary, following a common protocol recommended by the United Kingdom Coordinating Group for Predictive Testing in Huntington's Disease.[33] Results of the DNA test were not made available to the cognitive test administrator until all cognitive assessments had been completed.

Table 1 Demographic variables in AR+ and AR− groups

	AR+	AR−	Significance (p value)
Age	31·9 (10·3)	38·5 (11·4)	0·108
Education	11·8 (2·0)	11·6 (2·2)	0·875
Social class	3·1 (0·6)	3·1 (1·0)	0·951

Table 2 WAIS-R scores in AR+ and AR− groups

	AR+	AR−	Significance (p value)
Full Scale IQ	96·1 (12·3)	98·6 (12·3)	0·585
Verbal IQ	95·6 (12·5)	98·9 (15·5)	0·537
Performance IQ	97·8 (14·5)	99·8 (10·6)	0·671
Information	8·4 (3·0)	8·9 (2·9)	0·614
Digit Span	11·0 (3·3)	10·7 (3·2)	0·807
Vocabulary	9·1 (2·2)	10·4 (3·1)	0·179
Arithmetic	10·1 (3·5)	10·5 (3·4)	0·803
Comprehension	8·5 (2·3)	9·2 (2·6)	0·485
Similarities	9·1 (2·4)	9·6 (2·3)	0·564
Picture Completion	9·9 (3·2)	9·3 (2·9)	0·586
Picture Arrangement	9·5 (3·0)	10·8 (1·8)	0·162
Block Design	10·3 (3·3)	10·3 (2·6)	0·990
Object Assembly	9·8 (3·1)	10·6 (2·5)	0·487
Digit Symbol	8·6 (3·7)	9·9 (2·2)	0·269
NART Errors	25·7 (9·3)	19·2 (11·5)	0·100

Results

The DNA test results divided the at risk sample into two groups, with 13 in the AR+ group and 17 in the AR− group. Demographic variables for the two groups are presented in table 1. The mean age for the AR− group (38·5) was somewhat older than that for the AR+ group (31·9), a feature that would be expected given that a proportion of older gene carriers would in fact have developed the condition already. This age difference, however, did not reach statistical significance. Mean years of education for the two groups were 11·8 for the AR+ group and 11·6 for the AR− group. Again differences did not reach significance.

Results of the psychometric tests were analysed using *t* tests which compared group means. In order to reduce the possibility of type 1 errors the generally accepted level of significance (0·05) was divided by the number of planned comparisons to reach a new accepted level of significance of 0·001.

Mean data from the cognitive measures for the two groups is presented in tables 2 to 5. For ease of presentation test results are grouped according to the broad area of functioning being assessed. WAIS-R subtest scores given are age graded.

Tables 2 to 5 show a lack of between group differences in AR+ and AR− groups on a wide ranging battery of neuropsychological in-

Table 3 Executive/attention tasks in AR+ and AR− groups

	AR+	*AR−*	*Significance (p value)*
WCST Correct	35·9 (3·1)	33·7 (4·0)	0·120
WCST Perseverations	1·1 (1·4)	1·5 (3·0)	0·627
WCST Categories	5·8 (0·6)	5·3 (1·1)	0·147
Verbal Fluency F60	11·8 (4·5)	11·8 (4·3)	1·000
Verbal Fluency A60	8·7 (3·1)	11·3 (4·4)	0·082
Verbal Fluency S60	13·3 (4·3)	14·4 (3·8)	0·456
Verbal Fluency Perseverations Total	0·6 (1·0)	0·6 (1·3)	0·961
Cognitive Estimation Task	5·1 (3·7)	4·8 (3·5)	0·846
PASAT Total	147·5 (49·5)	131·1 (31·8)	0·352
PASAT Correct Consecutive Total	48·4 (41·2)	31·2 (20·2)	0·224
Trail A	33·8 (20·1)	27·0 (7·7)	0·306
Trail B	75·3 (46·8)	62·2 (17·3)	0·394

Table 4 Mnestic task performance in AR+ and AR− groups

	AR+	*AR−*	*Significance (p value)*
Digit Supraspan	3·2 (1·7)	3·6 (2·1)	0·633
Corsi Span	5·4 (1·4)	5·9 (0·9)	0·273
Corsi Supraspan	2·4 (0·8)	4·2 (1·6)	0·001
CVLT Free Recall List A Long and Short Delay	22·5 (7·1)	23·6 (4·4)	0·654
CVLT Cued Recall List A Long and Short Delay	23·3 (6·3)	25·3 (4·7)	0·388
CVLT Intrusions	4·8 (4·8)	2·7 (3·4)	0·221
CVLT Perseverations	5·9 (6·9)	6·4 (7·8)	0·854
CVLT Recognition – False Positives	13·7 (3·1)	14·1 (1·7)	0·650
Word Completion Previously Presented Items	8·7 (4·5)	9·3 (3·2)	0·708
Benton Visual Retention Test	11·8 (3·3)	13·5 (1·6)	0·150

Table 5 Visuospatial and motor task performance in AR+ and AR− groups

	AR+	*AR−*	*Significance (p value)*
Judgment of Line Orientation Corrected Score	23·2 (7·6)	24·3 (2·7)	0·640
Purdue Peg Board Total	116·2 (18·0)	126·0 (17·7)	0·168
Pursuit Rotor Mean Totals	59·7 (22·1)	48·3 (10·2)	0·136
Pursuit Rotor trials (5+6) − trials (1+2)	1·5 (0·2)	1·9 (0·5)	0·012
Finger Tapping	85·7 (14·4)	82·1 (18·1)	0·631

struments. Only one between group difference reached the required level of significance. Paradoxically, that is the difference in Corsi Supraspan, a task at which the AR+ group perform better. It is difficult to explain this finding but it is notable that the AR− group have a higher Corsi span (mean 5·9, SD 0·9) than the AR+ group (mean 5·4, SD 1·4). Although this between group difference is not significant, the difference in supraspan scores may reflect a ceiling effect in some AR− subjects.

The above findings suggest that a prodromal phase in Huntington's disease marked by cognitive decline has little experimental backing. This is in accordance with the findings of Strauss and Brandt.[14] However, if results are interpreted in the manner of Diamond *et al*[15] the position changes. Of the 47 measures the battery contains the AR− group are advantaged in terms of having a higher group mean, albeit insignificant, on 30 and the AR+ group advantaged on only 13. Using χ^2 this between group difference is significant at the 0·001 level ($\chi^2 = 11{\cdot}91$). This suggests that mild deficits may be apparent in at risk gene carriers and that tests used in the current battery are not sensitive enough to pick up between group difference.

Previous studies have suggested that deficits in at risk gene carriers are most apparent in mnestic tasks[15] and in skills associated with frontal lobe dysfunction.[13] Diamond *et al*[15] argue that the failure of the Strauss and Brandt[14] study to find between group differences for AR+ and AR− groups can be explained by the lack of mnestic tasks in their battery. The current study does not support such an argument. Although differences are not significant, the AR− group perform better on the California Verbal Learning Test and Benton Visual Retention Test measures and the AR+ group perform better on the Digit Span tasks and, significantly so, on the Corsi Supraspan task. The current study also does not support findings of early deficits in frontal lobe functioning of AR+ subjects. AR+ subjects have mean scores which are higher for the Wisconsin Card Sorting Test and the Paced Auditory Serial Addition Test, both tasks which are widely thought to involve significant frontal lobe activity.

Summary

Data from cognitive test results for at risk subjects in the current study provide little evidence to support the view that cognitive deficits are detectable in asymptomatic gene carriers. Only the Corsi Supraspan task showed a significant difference between groups, and paradoxically at risk gene carriers showed greater ability. However, while individual measures suggest only this between group difference, taken as a whole the study does suggest that minimal dysfunction may be apparent in asymptomatic AR+ subjects. Of the 47 measures included in the study, the AR− group are advantaged, in terms of having a higher group mean, on 30 and the AR+ group on only 13. It may be that deficits are detectable in individual gene carriers but that current measures of assessment are not sensitive enough to identify them at a group level.

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