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Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compared with controls: preliminary findings of the Edinburgh High Risk Study (EHRS)

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ABSTRACT

Background. Finding risk indicators for schizophrenia among groups of individuals at high genetic risk for the disorder, has been the driving force of the high risk paradigm. The current study describes the preliminary results of a neuropsychological assessment battery conducted on the first 50% of subjects from the Edinburgh High Risk Study.

Methods. One hundred and four high risk subjects and 33 normal controls, age and sex matched, were given a neuropsychological assessment battery. The areas of function assessed and reported here include intellectual function, executive function, perceptual motor speed, mental control/encoding, verbal ability and language, learning and memory measures, and handedness.

Results. The high risk subjects performed significantly more poorly than the control subjects in the following domains of neuropsychological function: intellectual function, executive function, mental control/encoding and learning, and memory. Controlling for IQ, high risk subjects made significantly more errors on the Hayling Sentence Completion Test (HSCT), took longer to complete section A of the HSCT, had lower scores on the delayed recall condition of the visual reproductions subtest of the Wechsler Memory Scale-Revised, and had significantly poorer Rivermead Behavioural Memory Test (RBMT) standardized scores. The presence of significant group by IQ interactions for the RBMT and time to complete section A of the HSCT suggested that differences among the groups were more marked in the lower IQ range. Performance on the HSCT was found to be related to the degree of family history of schizophrenia.

Conclusions. High risk subjects performed more poorly than controls on all tests of intellectual function and on aspects of executive function and memory.

INTRODUCTION

Schizophrenia is widely accepted to be a disorder of the brain (Weinberger, 1995). There are few certainties about the aetiology of the disorder, but a familial background and presumably genetic liability is certain to be important (Gottesman & Shields, 1976, 1982). Exactly what is inherited is the subject of much debate. There is evidence, from retrospective studies, to suggest that individuals who later develop schizophrenia display disturbances of motor development in infancy (Fish *et al*. 1992; Walker *et al*. 1993, 1994), and prospective studies show that they have language problems (Jones *et al*. 1994), and behavioural difficulties (Done *et al*. 1994) as children, suggesting the presence, however subtle, of continuous neurological deficit throughout childhood. If what is inherited is the propensity for the development of schizophrenia, as the balance of current evidence suggests, vulnerability markers in biological

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relatives of patients maybe very useful in identifying those at heightened risk for the disorder. Finding risk indicators for schizophrenia has been an endeavour of the high risk studies and studies of adult relatives of schizophrenic patients. High risk, in this context refers to the study of individuals who are considered to have a higher statistical risk of developing schizophrenia than members of the general population. Risk in this project, is based on genetic relatedness. The high risk paradigm typically involves the recruitment of children of patients with schizophrenia, with assessment at entry to the study and a long period of follow-up in a bid to closely identify the factors that lead to the development of schizophrenia in adult life (Asarnow, 1988; Cornblatt & Obuchowski, 1997 – for review and commentaries of high risk research). A difficulty with the high risk paradigm is that the follow-up period is often as much as 20 years and such studies have suffered greatly from high rates of attrition. Studies of the biological relatives of patients with schizophrenia usually involve a single assessment conducted in an attempt to measure the prevalence of deficits and possible markers in such populations.

It is well established that the diagnosis of schizophrenia is often accompanied by neuropsychological impairments (Bilder, 1996), specifically impairments of attention, memory, abstraction and mental flexibility or 'executive function' (Elliott & Sahakian, 1995; Elliott *et al*. 1995; Gur *et al*. 1997). A recent review of the evidence for neurocognitive deficits in schizophrenia based on 204 studies (Heinrichs & Zakzanis, 1998) concluded that schizophrenia is characterized by a broadly based cognitive impairment with differing degrees of impairment in many domains as measured on standard clinical tests. The role these impairments play in the pathogenesis of the disorder is less clear, whether they are an integral part of the illness or are a secondary effect of the other features remains uncertain. It has been difficult to find consistent correlations between demonstrated neuropsychological impairment and structural brain changes. It is well established that brain structure in groups of schizophrenic patients differs from that of groups of normal controls. Classical approaches have led to the suggestion that cognitive deficits in schizophrenia implicate dysfunction in frontal, temporal, limbic or integrated frontotemporal and frontolimbic systems (Bilder, 1996).

Neuropsychological dysfunction has been reported in relatives of schizophrenia patients (e.g. Faraone *et al*. 1995; Toomey *et al*. 1998). Specific domains of neuropsychological dysfunction have been identified. Areas that have been found to be impaired in relatives include sustained attention, perceptual motor speed, concept formation and abstraction/executive function, and mental control-encoding. Other deficits suggested are verbal fluency, verbal learning and memory (Faraone *et al*. 1995). The area of attention has been the focus of much research in high risk studies and in studies of adult relatives of schizophrenia patients. The present study aims to present the preliminary findings of the neuropsychological assessment of a group of young people at high genetic risk for the development of schizophrenia. The test battery chosen was designed to include tests which have been previously shown to differentiate subjects at high risk for schizophrenia and controls (Kremen *et al*. 1994), tests that have shown differences between schizophrenic patients and controls, and tests that localize to parts of the brain that have been shown on imaging or other investigations to differ between schizophrenia patients and controls. The battery was designed to be repeatable and not so prolonged that compliance would be reduced. These are the preliminary findings of an ongoing study.

Background to the Edinburgh High Risk Study

The Edinburgh High Risk Study (EHRS) was set up in 1994. The study was designed to follow young adults through an estimated 60% of their maximum risk period for developing schizophrenia, and over a 5-year period. This design redresses some of the difficulties of other high risk projects (Erlenmeyer-Kimling & Cornblatt, 1987). Recruitment in young adulthood prevents such high attrition rates from childhood to adulthood. The onset of schizophrenia most commonly occurs within this age group (Häfner & An Der Heiden, 1997). The change from risk and prodromal state to florid illness is not clearly understood, opportunities to study it have been few, however, it can be closely monitored in this investigation. It has the

advantage of being a study of adult relatives of patients with schizophrenia as well as being a high risk design. Differences between functional and behavioural patterns in childhood and adulthood preclude the generalization of findings in children to adults. This is avoided in the EHRS.

The sample under study comprises young persons aged between 16 and 25 years who have been identified to have at least two close members of their family suffering from schizophrenia, increasing their individual genetic risk for the disorder. It was intended that the study should concern 200 well young people from families where two or more people are affected by schizophrenia, (some from high density families, families that have multiple affected members), 30 normal controls without a family history of psychotic illness in either first- or second-degree relatives and 30 sporadic cases of schizophrenia. The groups are being followed up at 18 month intervals for 5 years. At each assessment subjects receive a detailed clinical assessment described in detail elsewhere (Hodges *et al.* 1999), structural brain imaging in the form of MRI scans (Lawrie *et al.* 1999) and detailed neuropsychological assessment, described here.

The overall aims of the study include the determination of the clinical, psychological, and neurological features, and detailed brain structures that distinguish those members of high risk families who develop schizophrenia from those who will not. We also seek to compare the results from these groups with other cases of first-episode schizophrenia and normal controls. The purpose of this paper is to describe the results of a neuropsychological assessment of the first 50% of the identified sample, at high genetic risk for schizophrenia, compared with normal controls.

METHOD

Subjects

This report does not consider the results of the neuropsychological assessments of the first-episode patients. Data collection is incomplete for the first episode patients to date due to difficulties in assessment of patients who are acutely psychotic. One hundred and four subjects (mean age 21·1 (S.D. 2·3), 51% male) were recruited from families where at least two close relatives of the subject were affected by schizophrenia. They were compared to 33 normal controls (mean age 21·2 (S.D. 2·8), 55% male), matched as closely as possible for age, sex and social class based on fathers occupation, who had no relatives with any psychotic disorder apart from dementia in old age. Details of the recruitment of the groups is outlined in Hodges *et al.* 1999. The demographic characteristics of the groups, including, age, sex, distribution of social class at birth and educational attainment are presented in Table 1. Social class at birth was based on father's occupation and information was collected from birth registrations. Social class was considered unclassifiable if there was no means of knowing the father's occupation at birth of the subject, or if the father was employed by the armed forces and the rank was unknown.

Neuropsychological assessment battery

A battery of neuropsychological assessments was administered to each individual. The tests were organized according to neuropsychological functions on the basis of general neuropsychological practice (Lezak, 1995), and in a manner similar to previous studies of adult relatives of patients with schizophrenia (Kremen *et al.* 1992, 1994). The tests administered and functions they serve to examine are outlined in Table 2. Most of the tests (1, 2, 4–8, 10–16) are well described elsewhere (Lezak, 1995; Spreen & Strauss, 1991). The Hayling Sentence Completion Test (HSCT, Burgess & Shallice, 1996) is a relatively new test. It is composed of two conditions, in both the sentence must be completed as quickly as possible with a one word answer. In the first condition, subjects are required to finish a sentence by inserting a word that sensibly completes the sentence. In the second condition subjects are required to give a ridiculous ending to the sentence by inserting a word that makes no sense in the context of the sentence (incongruous condition). The errors are scored according to the degree of sense made by the sentence completion. Category A errors are scored if a sentence in the incongruous condition is correctly completed. Category B errors are scored if the sentence makes some sense e.g. 'The whole town came to hear the Mayor……, answer: Sing.' Raw scores are then converted to scaled scores. Overall error scores were examined here. There are many

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Table 1. *Sociodemographic characteristics of the group*

	Controls ($N = 33$)		High risk ($N = 104$)		Test statistic	P
Age, mean (S.D.)	21·17	(2·25)	21·14	(2·83)	$t = 0·06$*	0·95
Gender, N (%)						
Male	17	(51·4)	57	(54·8)	$\chi^2 = 0·11$†	0·74
Female	16	(48·5)	47	(45·2)		
Social class at birth (fathers occupation), N (%)						
I and II	10	(30·3)	25	(24·0)		
III	16	(48·5)	52	(50·0)	$\chi^2 = 1·02$†	0·80
IV and V	4	(12·1)	19	(18·3)		
Unclassifiable	4	(9·1)	8	(7·7)		
Educational attainment N (%)						
Left school before 16 years	2	(6·1)	9	(8·7)		
Still at school	2	(6·1)	5	(4·8)		
GCSEs only	2	(12·1)	38	(36·5)	$\chi^2 = 2·45$‡	0·01
Highers only	4	(24·2)	14	(13·5)		
Certificate/diploma	8	(6·1)	16	(15·4)		
Entered university	2	(45.5)	22	(21.2)		
	15					

* Independent samples t test, two-tailed; † Pearson's chi-square statistic; ‡ Mann–Whitney U test.

Table 2. *Neuropsychological assessment battery*

Neuropsychological function	Tests
Current intellectual function	(1) Wechsler Adult Intelligence Scale Revised (WAIS-R; Wechsler, 1981)
Pre-morbid intellectual function	(2) National Adult Reading Test (Nelson & O'Connell, 1978; Nelson, 1982)
Executive function	(3) Hayling Sentence Completion Test (Burgess & Shallice, 1996) (4) Stroop Colour Word Test (computerized translation of Golden, 1978) (5) Verbal Fluency (FAS) and Semantic category, animals (Spreen & Strauss, 1991)
Perceptual motor speed	(6) WAIS-R Digit-symbol age scaled scores
Mental control/encoding	(7) WAIS-R Digit span age scaled scores (8) WAIS-R Arithmetic age scaled scores
Sustained attention	(9) Continuous Performance Test – Identical Pairs Version (CPT–IP) (Cornblatt *et al.* 1988)
Verbal ability and language	(10) Token test (Spreen & Benton, 1969, 1977) (11) WAIS-R Vocabulary age scaled scores
Learning and memory	
General memory	(12) Rivermead Behavioural Memory Test (Wilson *et al.* 1985)
Verbal learning	(13) Rey Auditory Verbal Learning Test (Rey, 1964)
Visual memory	(14) Wechsler Memory Scale – Revised, Visual Reproductions, immediate and delayed conditions (Wechsler, 1987)
Verbal memory	(15) Rivermead Behavioural Memory Test Story, immediate and delayed conditions (Wilson *et al.* 1985)
Handedness	(16) Annett Handedness Scale (Annett, 1970) and the Edinburgh Handedness Inventory (Oldfield, 1971)

variants of the continuous performance test which have been used extensively to evaluate the role of sustained attention in schizophrenia. The Continuous Performance Test – Identical Pairs (CPT–IP) version (Cornblatt *et al.* 1988) was used here and is a cognitively challenging form of the task. In high risk research more difficult forms of the CPT have provided evidence to suggest that attentional deficits may be markers for a genetic liability to schizophrenia (Rutschmann *et al.* 1977; Nuechterlein, 1983; Cornblatt & Erlenmeyer-Kimling, 1985). The

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CPT–IP takes the form of presenting a series of numbers and shapes (in separate conditions), to test both visual and spatial processing capabilities. Subjects were required to respond whenever two identical stimuli appeared in a row. The CPT–IP is well described elsewhere (Cornblatt *et al*. 1988). First, numbers were presented without any distraction, the stimulus appeared on the screen for 50 ms followed by a dark screen for 950 ms. The numbers condition was followed by the shapes condition, presented in an identical manner. The purpose of these two conditions was to assess if there was a deficit in sustained attention. Next, numbers and shapes were again presented at the same rate, this time in the presence of both visual and auditory distractions. The purpose of these conditions was to assess for evidence of abnormal distractibility. In all conditions there were 30 target trials, 30 close but not exact matches termed 'colds', and 90 random unrelated stimuli called 'filler' trials. Three performance measures of the CPT–IP were analysed. These included two signal detection indices, d′, to measure declines in sensitivity and attentional capacity, β, to measure shifts in response style or tendency to over respond *versus* under respond, converted to the natural log scale ($\ln \beta$) and also random errors on the task converted to the natural log scale (ln randoms) (Cornblatt *et al*. 1988). All performance measures were calculated by the CPT-IP software.

Statistical analyses

Given that gender differences have been demonstrated in cognitive function in patients with schizophrenia (Lewine *et al*. 1997) and in relatives (Kremen *et al*. 1997) of such patients, a gender by group (whether high risk or control) analysis of variance (ANOVA) was conducted for the individual test scores. Analyses were conducted separately for males and females where group by gender interactions were found. An inequality between the groups in terms of IQ was revealed in the initial analysis. Given the likely effect of IQ on neuropsychological test results, an analysis of covariance (ANCOVA) was performed with WAIS-R Full Scale IQ as a covariate wherever a main effect for group was found in the initial analysis. The purpose was to identify whether the group differences suggested in certain domains of function, were independent of IQ. All ANCOVAs were performed using the General Linear Model option of SPSS 7.5 for Windows (SPSS, 1996). The ANCOVA model, included group (whether high risk or control) as a factor, with Full Scale IQ as the covariate, and a group × IQ interaction term. For data that was not normally distributed ANCOVAs were conducted on the ranked dependent variable and the ranked covariate (Conover & Iman, 1982), with a group × IQ interaction term also included in the model. For the continuous performance test the research questions 'Is there a difference between the groups on measures of sustained attention?' and 'Is there a difference between the groups in terms of distractibility?' were answered by submitting the three performance measures, d′, ln β and ln randoms to a 2 (group; high risk *versus* control) by 2 (distraction; no-distraction *versus* distraction) by 2 (stimulus; numbers *versus* shapes) repeated measures ANCOVA with WAIS-R Full Scale IQ as a covariate. The summary statistics presented in the tables take the form of means and standard deviations for normally distributed data, medians with the 25th and 75th percentiles for the non-normal data. In the case of the HSCT times on section A, the data were transformed to normal using a log transformation, the geometric mean and the 95% confidence interval calculated on the log scores and converted back to the original scale is presented (Altman *et al*. 1983). Non-parametric analyses were conducted where the scores were categorical or were not normally distributed and suitable transformations to normality could not be found. All analyses were conducted using SPSS 7.5 for Windows (SPSS, 1996).

RESULTS

The results are organized by domain of function, the results of the initial analyses are displayed in Table 3 and the results of the CPT–IP are displayed in Table 5.

Intellectual function

High risk (HR) subjects demonstrated significantly lower scores on all measures of current intellectual and pre-morbid intellectual function. HR subjects had a significantly ($P = 0{\cdot}01$) lower mean verbal IQ, mean performance IQ ($P = 0{\cdot}01$) and mean full scale IQ ($P = 0{\cdot}05$) com-

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Table 3. *Comparison of neuropsychological functioning in controls and high risk*

	Controls ($N = 33$) Mean (S.D)	High risk ($N = 104$) Mean (S.D.)	Main effects of group	
			F	P
Current intellectual function				
Verbal IQ	102·54 (12·68)	97·77 (11·82)	4·05	0·05
Performance IQ	107·48 (16·09)	99·78 (14·26)	7·05	0·01
Full Scale IQ	105·15 (14·22)	98·48 (13·05)	6·47	0·01
Pre-morbid intellectual function				
National Adult Reading Test – Full Scale IQ	104·88 (8·22)	98·69 (10·01)	9·72	0·002
Executive function				
Stroop colour word test, interference condition	21·42 (5·12)	23·24 (5·19)	2·97	0·09
Verbal fluency				
FAS	40·18 (9·56)	38·69 (12·74)	0·39	0·53
Semantic category animals	17·94 (6·41)	16·08 (4·77)	3·32	0·07
Hayling response times on section A*	14·36 (12·57, 16.46)	18·45 (16·60, 20·60)	5·04	0·03
Hayling Error Score†	3·00 (0·5, 5·00)	5·00 (1, 18·25)	$z = 2·46$	0·01
Perceptual motor speed				
WAIS-R digit symbol age scaled scores	11·27 (2·75)	10·19 (2·84)	3·32	0·07
Mental control/encoding				
WAIS-R digit span forward age scaled scores	8·21 (2·29)	8·50 (2·18)	0·46	0·50
WAIS-R digit span backward age scaled scores	7·76 (2·33)	7·18 (2·33)	1·67	0·20
WAIS-R arithmetic age scaled scores	10·12 (3·02)	9·37 (2·45)	2·04	0·16
WAIS-R arithmetic‡				
Males	11·47 (2·76)	9·51 (2·61)	7·19	0·01
Females	8·69 (2·65)	9·21 (2·24)	0·60	0·44
Verbal ability and language				
WAIS-R Vocabulary age scaled scores	9·30 (1·85)	8·51 (2·36)	3·00	0·09
Token test (overall total)†	163·00 (162, 163)	163·00 (161, 163)	$z = 1·70$	0·09
Learning and memory				
RAVLT				
Total of conditions 1–5	54·73 (8·49)	50·85 (8·81)	4·50	0·04
Delayed recall	11·79 (2·55)	10·20 (2·81)	7·94	0·01
WMS-R Visual reproductions				
Total immediate recall	37·40 (2·79)	35·72 (4·12)	3·62	0·06
Total delayed recall	35·40 (4·55)	32·85 (5·96)	3·88	0·05
Rivermead Behavioural Memory Test				
Standardized score†	22·00 (21·5, 24)	22·00 (20, 24)	$z = -1·97$	0·05
Asymmetry: Handedness				
Right-handed	$N = 30$ (91%)	$N = 92$ (88·5%)	$\chi^2 = 0·15$	0·69
Left-handed	$N = 3$ (9%)	$N = 12$ (11·5%)		

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.

† Data not normally distributed and analysed using non-parametric Mann–Whitney U test, medians (25th and 75th percentiles) presented.

‡ Group by gender interaction, analysis conducted separately for males and females.

pared with the control subjects. HR subjects had significantly ($P = 0·002$) lower mean NART full scale IQ estimates compared to controls.

Executive function

There was a trend ($P = 0·09$) for controls to achieve faster times in the interference condition of the Stroop test compared with the HR subjects. There was no significant difference between the groups in terms of verbal fluency, as measured by the FAS test. There was a trend ($P = 0·07$) for controls to produce the names of more four-legged animals than HR subjects. HR subjects were poorer than controls on measures of the Hayling Sentence Completion Test (HSCT). As the error scores were not normally distributed the initial analysis was performed using non-parametric methods, the median error score (25th and 75th percentiles) is presented in Table 3. High risk subjects made significantly ($P = 0·01$) more errors than controls. The time in seconds to sentence completion in section A of the HSCT was transformed to a normal distribution using a natural log transformation.

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Table 4. *Analysis of covariance investigating the effect of full scale IQ on neuropsychological test performance, where initial analysis revealed significant* ($P \leqslant 0{\cdot}05$) *group differences*

	Main effect for group		Main effect of covariate full scale IQ		Group, full scale IQ interaction	
	F	*P*	*F*	*P*	*F*	*P*
Executive function						
Hayling response times on section A*	5·06	0·03	1·40	0·24	4·13	0·04‡
Hayling error score†	5·09	0·03	3·68	0·06	2·48	0·12
Learning and memory						
RAVLT						
Total of conditions 1 to 5	0·39	0·53	33·55	< 0·001	0·23	0·63
Delayed recall	1·24	0·27	14·35	< 0·001	0·71	0·40
WMS-R						
Visual reproductions	3·75	0·05	36·18	< 0·001	3·37	0·07
Total delayed recall						
Rivermead Behavioural Memory Test standardized score†	6·36	0·01	9·29	0·003	5·08	0·03§

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.

† Data not normally distributed and analysed using non-parametric Mann–Whitney *U* test, medians (25th and 75th percentiles) presented.

‡ See Fig. 1.

§ See Fig. 2.

The results (see Table 3) suggest that the HR subjects were significantly ($P = 0{\cdot}03$) slower than controls on this task (the geometric mean with a 95% CI calculated on the log scores and converted back to the original scale are presented here.

Perceptual motor speed

There was a trend ($P = 0{\cdot}07$) for HR subjects to achieve lower digit symbol scaled scores than controls (see Table 3).

Mental control/encoding

There were no differences between HR subjects and controls in terms of WAIS-R digit span forwards or backwards. There was no overall group effect for WAIS-R arithmetic scaled scores. Due to the presence of a group by sex interaction for arithmetic analysis was conducted separately for males and females. The results revealed that male HR subjects achieved significantly lower ($P = 0{\cdot}01$) arithmetic scores than male controls. There was no significant difference for females.

Verbal ability and language

There was a trend ($P = 0{\cdot}09$) towards lower mean WAIS-R vocabulary scores for HR subjects compared to controls. There was also a trend ($P = 0{\cdot}09$) for HR subjects to achieve poorer scores on the Token Test compared with controls.

Learning and memory

HR subjects performed more poorly than controls on all measures of learning and memory. HR subjects learned and remembered significantly ($P = 0{\cdot}04$) fewer words across all five trials of the RAVLT than controls. They remembered significantly ($P = 0{\cdot}01$) less words on the delayed recall section of the RAVLT. There was a trend ($P = 0{\cdot}06$) towards poorer scores among the HR subjects compared with the controls on the visual reproductions subscale of the WMS-R for the immediate condition and HR subjects performed significantly ($P = 0{\cdot}05$) worse on the delayed recall section of this task. The HR subjects had significantly ($P = 0{\cdot}05$) lower standardized scores on the RBMT compared with controls, the median (25th and 75th percentiles) is presented in Table 3.

Handedness

There was no difference between the groups in terms of hand preference classified here as preferred hand for writing.

The results of the analysis of covariance are presented in Table 4. Controlling for IQ a significant main effect for group was noted (with no group by IQ interaction) for HSCT error scores ($P = 0{\cdot}03$) and the delayed recall condition of the WMS-R visual reproductions ($P = 0{\cdot}05$), where the performance of the high risk

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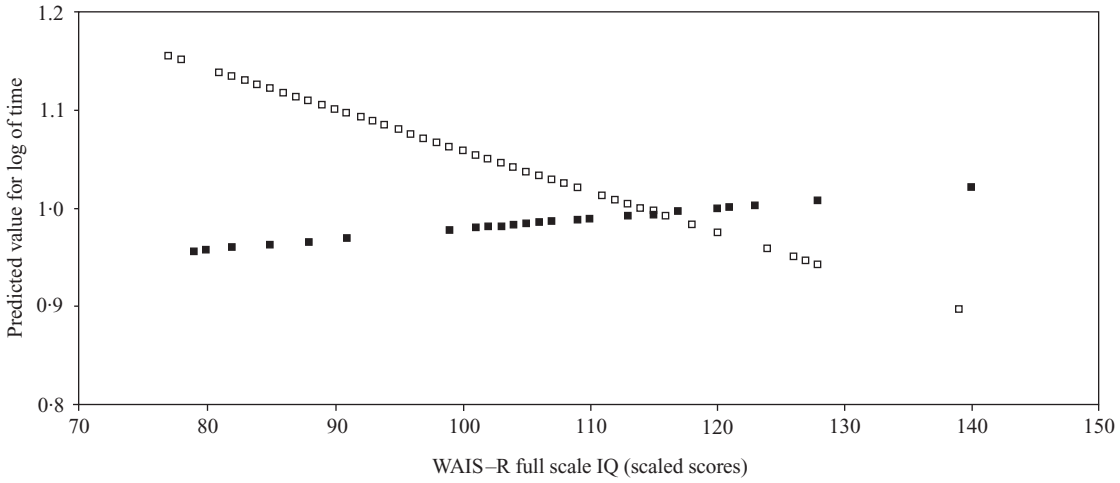

FIG. 1. Scatter plot of predicted values for the log transformed time values for the Hayling Sentence Completion Test, section A (□, high risk; ■, control).

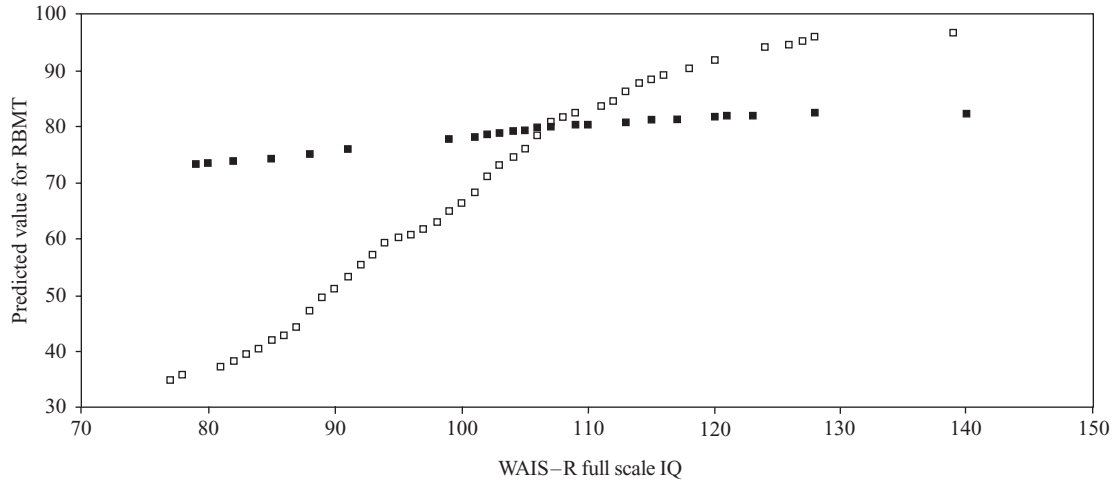

FIG. 2. Scatter plot of predicted values for the ranked standardized scores of the Rivermead Behavioural Memory Test (□, high risk; ■, control).

group was poorer than that of the control group on these tasks. A significant main effect for group was found for the Rivermead Behavioural Memory Test standardized scores ($P = 0{\cdot}01$) and for the response times for HSCT section A ($P = 0{\cdot}03$), with the high risk group performing more poorly than the control group, however, significant group by IQ interactions were found making the interpretation of the main effect less clear. The interactions are graphically presented in Figs. 1 and 2. A scatter plot of the predicted values from the ANCOVA model for the log-transformed time values for section A of the HSCT, plotted against WAIS-R Full Scale IQ is presented in Fig. 1. In Fig. 2 the predicted values for the ranked standardized scores of the RBMT were plotted against WAIS-R Full Scale IQ. The residuals from both models were normally distributed. The model predicted the HR group to perform more poorly than the control subjects on the RBMT in the lower range of IQ but better than the control group when IQ increased beyond 110. A similar result was found for the HSCT, time on section A, where the HR group

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Table 5. *Summary statistics for the Continuous Performance Test–Identical Pairs version*

	Controls Mean (S.D.)	High risk Mean (S.D.)	Group effect controlling for IQ* *F*	*P*
d′				
Numbers				
Fast no distraction	1·96 (0·88)	1·83 (0·84)		
Fast distraction	1·67 (0·78)	1·70 (0·91)		
Shapes			0·29	0·59
Fast no distraction	1·93 (0·58)	1·70 (0·71)		
Fast distraction	2·29 (0·79)	1·93 (1·80)		
Log beta				
Numbers				
Fast no distraction	−0·37 (0·77)	−0·30 (0·72)		
Fast distraction	−0·04 (0·54)	−0·01 (0·73)		
Shapes			0·04	0·85
Fast no distraction	−0·14 (0·63)	−0·23 (0·74)		
Fast distraction	−0·23 (0·96)	−0·20 (0·80)		
Log randoms				
Numbers				
Fast no distraction	0·19 (0·40)	0·48 (0·63)		
Fast distraction	0·40 (0·51)	0·61 (0·60)		
Shapes			0·83	0·36
Fast no distraction	0·37 (0·51)	0·50 (0·64)		
Fast distraction	0·35 (0·49)	0·55 (0·73)		

* The *F* and *P* values come from a 2 Group (High risk *versus* Control) × 2 Stimulus (Shapes or Numbers) × 2 Distraction (distraction *versus* no distraction) analysis of covariance with WAIS-R full scale IQ as a covariate. There were consistent and significant effects of IQ for d′ and ln randoms but not for ln beta. There were no two-way interactions involving groups.

Table 6. *Neuropsychological assessment results: analysis by family history*

	Absent (*N* = 33)	Second degree (*N* = 29)	First and second degree (*N* = 63)	More than one first degree (*N* = 10)	F/χ^2	*P*
Executive function						
HSCT response times to section A*	14·36 (12·57–16·46)	20·79 (16·62–26·59)	17·42 (15·37–20·43)	16·01 (12·96–19·95)	2·45†	0·09
HSCT total error Score‡	3·00 (0·5, 5·00)	4·00 (1·00, 11·00)	5·00 (1·00, 19·00)	14·50 (4·75, 21·50)	9·61§	0·02
Memory tests						
RBMT standardized score§	22·00 (21·00, 24·00)	22·00 (20·00, 20·00)	22·00 (20·00, 24·00)	21·50 (18·75, 23·25)	4·99§	0·17
WMS-R Visual Reproductions delayed recall, Mean (S.D.)	35·40 (4·55)	34·11 (5·11)	32·17 (6·28)	33·44 (6·23)	2·29†	0·08
Full scale IQ, Mean (S.D.)	105·15 (14·22)	100·37 (11·05)	97·94 (13·84)	96·30 (14·01)	2·39†	0·07

* Analysis conducted on the natural log of response times for section A, geometric mean times presented here, with 95% CI for the mean calculated on the log scale and converted back to the original.
† Parametric oneway ANOVA.
‡ Medians (25th and 75th percentiles) presented.
§ Kruskall–Wallis oneway ANOVA.

were predicted to take longer than controls to complete the task when IQ was in the lower range but the opposite was true when IQ increased above 116.

The results of the CPT–IP are presented in Table 5. We did not find any main effect for group for any of the performance indices (Table 5). There were no two-way interactions involving group, suggesting that there were no differences between the high risk and control group on any of the performance measures of the CPT–IP measuring sustained attention or distractibility. There were consistent and significant effects of IQ for d′, and ln randoms but not for $\ln \beta$.

The degree to which measures of the Hayling Sentence Completion Test, the RBMT and the WMS-R visual reproductions delayed recall condition were related to family history of

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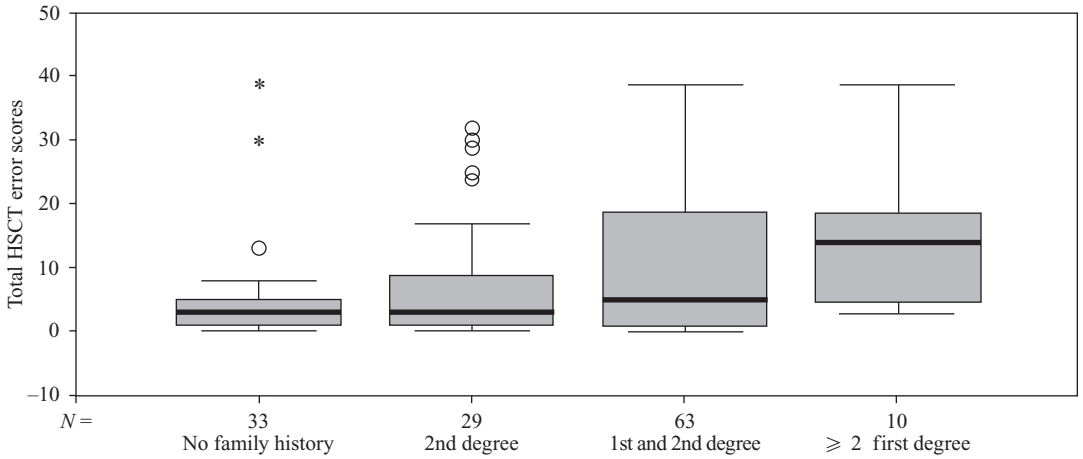

FIG. 3. Profile of HSCT error scores by family history groupings (○, an outliers – defined as a case with values between 1·5 and 3 box-lengths from the upper or lower edge of the box; *, an extreme value – defined as a case with a value > 3 box-lengths from the upper or lower edge of the box (see SPSS, 1996)).

schizophrenia, was investigated (given that the results of these tests seem to be related to subject status, whether HR subject or control). For the purposes of this analysis, degree of family history for schizophrenia was defined as: no family history (controls); at least two second-degree relatives affected; one first-degree relative and at least one other second-degree relative affected; at least two first-degree relatives affected. There was a non-significant trend ($P = 0{\cdot}07$) towards a difference across family history groups in terms of full scale IQ. The analysis involving family history groups was, therefore, not stratified by IQ as the difference was not significant. The results are described in Table 6.

There was a relationship between family history and Hayling error scores (Fig. 3), with those with two or more first-degree relatives performing significantly more poorly than the other groups and all groups performing worse than controls in terms of overall errors ($P = 0{\cdot}02$). There were no significant differences for any other measures.

DISCUSSION

The results to date show that for many of the neuropsychological assessments there was at least a trend towards poorer performance among the HR group compared to the controls (Table 3). Preliminary results of a battery of neuropsychological assessments are presented here for a relatively small but highly specialized, and we feel, very important sample. We were interested in investigating the possible presence of neuropsychological deficits among the HR group compared to the controls in a number of domains of function as outlined in Table 2. Finding significantly lower group performances among HR group (which is probably heterogeneous) compared with the controls in any domain of function is important as it hints at possible areas of vulnerability that may be especially marked in some subgroups. Neuropsychological deficits in this young well population were expected to be subtle, otherwise such individuals would be presenting for treatment of clinically relevant impairments, which would be disruptive to vocational and social functioning. It is for the above reasons that correction of multiple comparisons have not been made. Many areas of functioning were tested, but each was decided *a priori*. We were interested in assessing all domains individually and not the general null hypothesis (Perneger, 1998). Our results agree with the findings of previous HR research and indicate vulnerability in areas implicated in schizophrenia, namely executive function, memory and general intellectual performance.

The most striking finding was the general intellectual disadvantage of the HR group

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compared with the control group, as evidenced on all measures of intellectual functioning. This discrepancy in IQ between the groups explained some of the differences found on the other neuropsychological tests. Controlling for IQ and IQ by group interactions, group differences remained for the HSCT error scores, time to complete section A of this test, delayed recall of the visual reproduction subtest of the WMS-R and the RBMT standardized scores (Table 4). The initial group differences found for the RAVLT were overwhelmingly accounted for by the differences in IQ among the groups, suggesting that performance on this test of verbal memory and learning is positively related to intellectual capability and not related to genetic risk for schizophrenia. There have been previous reports of lower IQ in childhood among those at risk for schizophrenia compared with controls (e.g. Offord & Cross, 1971; Neale, 1984) and this finding has been interpreted as the possible presence of minimal brain damage in the pre-schizophrenic group (Offord & Cross, 1971). Jones *et al*. (1994) found that low educational test scores at ages 8, 11 and 15 were risk factors for the later development of schizophrenia and were not explained by social class. Results from the New York High Risk project suggested that those at high risk for schizophrenia had lower IQ scores at ages 7 and 9 compared with subjects at high risk for affective disorders (Ott *et al*. 1997). The finding of reduced IQ scores in the HR group compared to a control group is not new and confirms previous reports. The group by IQ interactions for the RBMT standardized scores and the HSCT times to complete section A, make the interpretation of the main effect for group difficult. The predicted values from the models with significant group by IQ interactions, plotted against Full Scale IQ, are presented in Fig. 1 for time on section A of the HSCT and in Fig. 2 for the RBMT standardized scores. Both scatter plots show that the greatest predicted differences between the groups exists in the lower IQ range, suggesting that IQ may be a modifying variable in the relationship between group and these neuropsychological measures. Previous studies have suggested that having a lower IQ may be a risk factor for the development of schizophrenia (e.g. Ott *et al*. 1997; Erlenmeyer-Kimling *et al*. 1984; Jones *et al*. 1994). It does not appear to be a lower IQ *per se* that is the problem as the controls within the lower IQ range do not show the same disadvantage on the RBMT, or on the time to complete the HSCT section A. From Figs. 1 and 2 it can be seen that the slope of the line for the predicted values for the controls is slight compared with the slope for the HR group. Also, HR subjects with higher IQs had predicted values greater than the controls on these measures, although the magnitude of the differences was not so marked. This may indicate that having a higher IQ is somewhat protective against impairment in these domains of function in the HR group. While there was no significant group by IQ interaction for the HSCT error scores the profile of the plotted predicted values are very similar with the largest differences between the HR and control groups occurring in the lower IQ range. The Hayling Sentence Completion Test is a new test, which has been used with success to identify groups of patients with frontal lobe dysfunction (Burgess & Shallice, 1996). The findings of the Hayling Sentence Completion test suggest that the HR subjects, especially those with lower IQs, are poorer at this test of executive function. This is in keeping with previous findings of executive dysfunction in patients with schizophrenia (Elliott & Sahakian, 1995; Elliott *et al*. 1995). We did not find any significant group differences on the other measures of executive function, measures of verbal fluency, or the Stroop test. There was a trend ($P = 0{\cdot}09$) for the control group to achieve faster times on the Stroop than the HR group in the initial analysis. Active cognitive inhibition is required for good performance on both the HSCT and the Stroop. The version of the Stroop that we used was a shortened computerized version of the paper and pencil test, and it became apparent during testing that this test did not prove to be very challenging to the subjects; on the other hand most subjects reported the HSCT to be a challenging task. It could be that subtle difficulties with this aspect of executive function, i.e. cognitive inhibition exists in some members of the HR group in the lower IQ range.

Another interpretation of our findings is that those HR subjects with lower IQs have a general intellectual deficit which impacts on aspects of memory and executive function in a manner different to the analogous normal controls. It

could be that there is a different underlying mechanism in the two groups. Reduced IQ in the individuals with a high genetic risk for schizophrenia was accompanied by deficits in other areas of neuropsychological functioning which was not so marked in normal control subjects. Perhaps this general deficit is inherited as part of the schizophrenic genotype and represents the presence of minimal brain damage as suggested previously (Offord & Cross, 1971) in some subjects at high risk for the development of schizophrenia.

Poor performance on the Hayling Sentence Completion Test was related to family history for schizophrenia. Clearly, the more first-degree relatives affected, the poorer the performance (see Table 6). Similar findings in this sample were found in respect of brain structure, particularly the volume of the third ventricle was significantly increased in the HR subjects with higher genetic loading (Lawrie *et al*. 1999).

We found no differences between the groups in terms of sustained attention, unlike other high risk studies (Rutschmann *et al*. 1977; Nuechterlein, 1983; Cornblatt & Erlenmeyer-Kimling, 1985). The difference between the cited studies and ours being that they were conducted on young children at risk for schizophrenia whereas our HR group are young adults. Cornblatt & Erlenmeyer-Kimling (1984) reported no differences between HR and control subjects on a high demand CPT task in subjects between 13 and 18. Within their sample they reported poorer performance on the task for the 13–14-year-old HR subjects when compared with same age normal controls. The authors interpreted the absence of group differences to reflect age ceiling effects on the CPT.

Faraone *et al*. (1995) reported no differences between relatives of schizophrenic patients and controls on a measure of auditory CPT when both groups were in their mid 30s. In our sample all subjects, both HR and control, commented on the difficulty of the task and we did not find ceiling effects. It may be that sustained attention improves with age and that in the absence of any clinical features or prodromal features of psychosis, there is no evidence for deficits in sustained attention in young adult HR subjects compared with normal controls.

It was noted through the course of testing and analysis that some of the tests proved to be fairly unchallenging to the subjects, particularly the Token Test, and our computerized version of the Stroop, suggesting that these tests may not be sensitive enough to distinguish true differences between the groups in their respective domains of function. In November 1997, nine subjects had psychotic symptoms on Present State Examination (Symptoms 49–92; Wing *et al*. 1974), fully held in four cases, partially held in a further five cases. These findings are very preliminary but at present our interpretation is that certain behavioural and psychopathological characteristics described elsewhere (Hodges *et al*. 1999; Johnstone, 1998) may predict the development of the psychosis while poor performance on some executive and memory tests, set against a background of lower IQ scores and structural abnormalities (Lawrie *et al*. 1999) may indicate inheritance of the genotype.

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