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Different vulnerability indicators for psychosis and their neuropsychological characteristics in the Northern Finland 1986 Birth Cohort

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This study is one of very few that has investigated the neuropsychological functioning of both familial and clinical high risk subjects for psychosis. Participants ($N = 164$) were members of the Northern Finland 1986 Birth Cohort in the following four groups: familial risk for psychosis ($n = 62$), clinical risk for psychosis ($n = 20$), psychosis ($n = 13$), and control subjects ($n = 69$). The neurocognitive performance of these groups was compared across 19 cognitive variables. The two risk groups did not differ significantly from controls, but differed from the psychosis group in fine motor function. Neuropsychological impairments were not evident in a non-help-seeking high-risk sample.

Keywords: Neuropsychology; Neurocognition; Cognition; Profile; Psychosis; Psychosis risk; Familial risk; Clinical risk; Birth cohort; General population.

Psychoses are considered to be one of the most disabling mental health problems (Andreasen, 2001), and they tend to become overtly manifest in adolescence and early adulthood (Paus, Keshavan, & Giedd, 2008). In recent years, considerable research effort has been dedicated to the detection of psychosis in its earliest stages, in the hope that prompt interventions in psychotic illness or even in those at risk for psychotic illness might lead to improved long-term outcomes. Cognitive functioning is known to be impaired in both the premorbid and prodromal state of psychosis and may be seen as a relevant entity in regard to etiology of the disorder (Brewer et al., 2006; M. Cannon et al., 2006; Erlenmeyer-Kimling et al., 2000; MacCabe, 2008; Snitz, Macdonald, & Carter, 2006). However, the results concerning specific cognitive deficits are rather inconsistent, a fact that may arise, at least partly, from differences in methodological and sample characteristics.

Two main approaches exist for defining heightened risk for psychosis: the familial/genetic approach and the clinical high risk approach. In the former approach a heightened risk for a psychosis exists if a person

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has a family history of psychosis and thus presumed genetic risk (Goldstein, Buka, Seidman, & Tsuang, 2010; Gottesman, 1991). A clinical high risk of psychosis exists if a individual manifests subthreshold psychotic symptoms. Different transition rates have been published based on these differently defined risk subjects. Individuals with a parent with psychosis have, in general, a 10% lifetime risk of developing psychosis (Sullivan, 2005). In the studies on clinical high risk of psychosis, transition rates between 21% to 54% for the risk of developing psychosis within 1–2 years of follow-up have been reported (T. D. Cannon et al., 2008; Miller et al., 2002; Yung et al., 1996; Yung, Phillips, Yuen, & McGorry, 2004). Different predictive models have been developed but it is not yet possible, at least not satisfactorily, to predict who will go on to develop psychosis.

Neuropsychological indicators may provide one possibility for better prediction models, and to date some promising results have already been published (Becker et al., 2010; Brewer et al., 2005; Lencz et al., 2006; Wood et al., 2008). However, more research is needed before any clinically meaningful application for the prediction of psychosis can be developed. For example, it is not yet known whether there is a general cognitive signature of risk for psychosis, or whether specific risk factors for psychosis are associated with specific cognitive profiles. Although several studies have examined cognition in subjects at high risk for psychosis for clinical reasons (Brewer et al., 2005; Eastvold, Heaton, & Cadenhead, 2007; Frommann et al., in press; Gschwandtner et al., 2006; Keefe et al., 2006; Lencz et al., 2006; Pflueger, Gschwandtner, Stieglitz, & Riecher-Rossler, 2007; Pukrop et al., 2007; Pukrop et al., 2006; Wood et al., 2003), or cognitive function in subjects at risk for psychosis due to having a family history (Barrantes-Vidal et al., 2007; Cosway et al., 2002; Delawalla et al., 2006; Franke, Gansicke, Schmitz, Falkai, & Maier, 1999; Klemm, Schmidt, Knappe, & Blanz, 2006; Scarone, Abbruzzese, & Gambini, 1993; Seidman et al., 2006; Wolf, Cornblatt, Roberts, Shapiro, & Erlenmeyer-Kimling, 2002), to date, very few studies have compared cognitive function in these two groups (Myles-Worsley et al., 2007; Seidman et al., 2010).

In order to know which cognitive functions are impaired and to what degree in different risk groups and which functions remain intact, we investigated the neuropsychological profiles of two different vulnerability groups derived from the same general population birth cohort: familial and clinical risk groups. For comparison we used a group of subjects with psychosis and a group of general population controls sampled from the same cohort, having been born in the same year and in the same area as the index subjects.

METHOD

Study sample

The subjects of the study were derived from the Northern Finland 1986 Birth Cohort (NFBC 1986; Järvelin, Hartikainen-Sorri & Rantakallio, 1993; see Figure 1). NFBC 1986 consists of children with the expected date of birth between July 1, 1985, and June 30, 1986, in the two northernmost provinces of Finland (Järvelin, Hartikainen-Sorri, & Rantakallio, 1993). A total of 9,432 live-born children were born into the cohort, of whom 9,332 were alive on January 1, 2006. A field study surveying risk for psychosis took place between 2007 and 2009 for a subsample of the members of the NFBC 1986 when participants were in their early twenties (mean age = 22.8 years, $SD = 0.8$ years). For the field survey we invited subjects with familial risk (FR) for psychosis and symptomatic risk for psychosis, patients with established diagnosis of a psychosis, and control subjects without familial risk and without symptomatic risk for psychosis (see Figure 1).

Invited subjects

Subjects with psychoses

All cohort members who after the age of 12 years had hospitalizations due to psychotic disorder or A-type personality disorder according to the Finnish Hospital Discharge Register (FHDR) or who had free medication for psychosis according to the National Social Insurance Institute until the end of year 2005 were invited to participate in the study.

Subjects with familial risk (FR) for psychosis

All cohort members who had a parent with psychosis or A-type personality disorder according to the FHDR between 1972 and 2005 were invited to participate in the study (familial risk group).

Subjects with symptomatic risk for psychosis

All those who met specific criteria for high risk for psychosis due to various psychosis-like symptoms in the Youth Self Report (Achenbach, 1991) and PROD-screen (Heinimaa et al., 2003) and had functional decline at the time of earlier follow-up of this cohort at the age 15–16 were invited (for detailed invitation criteria see Veijola et al., 2010).

Control group

A random sample of the rest of the cohort members (who did not meet eligibility criteria for any of the above three groups) were invited as a control group.

Written informed consent was obtained from all participants. The study has been approved by the Ethics Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland, on May 24, 2006.

Exclusion criteria for all groups

Exclusion criteria were used for all groups as follows: estimation of full-scale intelligence quotient, FSIQ < 70 according to verbal and nonverbal subtests from

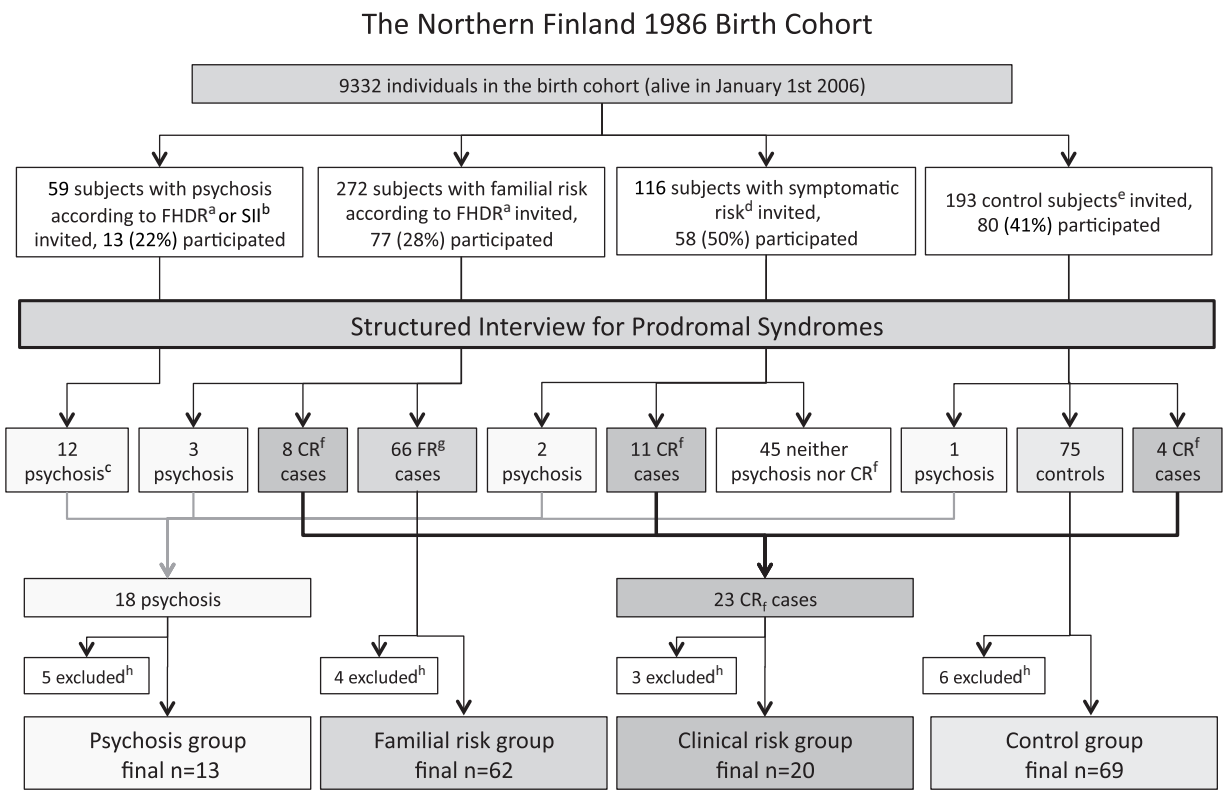

Figure 1. The Northern Finland 1986 Birth Cohort. [a]The Finnish Hospital Discharge Register. [b]The Social Insurance Institute of Finland. [c]One of the 13 subjects did not fulfill the criteria for psychotic disorder. [d]See the text and Veijola et al. (2010) for criteria. [e]Not meeting the criteria for any other group that were invited. [f]Clinical risk for psychosis. [g]Familial risk for psychosis. [h]See the text for exclusion criteria.

the Wechsler Adult Intelligence Scale–Third Edition (WAIS–III: Vocabulary and Matrix Reasoning, respectively; Wechsler, 1997), or mental retardation according to the FHDR or previous studies on this cohort (Heikura et al., 2003), neuropsychiatric syndromes such as attention-deficit/hyperactivity disorder according to FHDR or previous study on this same cohort (Smalley et al., 2007), autism spectrum disorders or speech development disorder with evident cognitive sequelae based on the FHDR, and neurologic conditions such as epilepsy and multiple sclerosis according to the FHDR.

Included participants ($N = 164$)

In the field study in 2007–2009 the current psychosis risk status of participant was assessed with the Structured Interview for Prodromal Syndromes (SIPS; McGlashan et al., 2001; Miller et al., 2003; Miller et al., 2002; Figure 1). The SIPS is a semistructured interview that identifies clinical risk (CR) status on the basis of the presence of attenuated psychotic symptoms, brief, limited and intermittent psychotic symptoms, and/or genetic risk with recent functional deterioration. The research groups were ascertained based on this interview. One member of the invitation group of psychosis and 45 subjects from the group of symptomatic risk did not fulfill the SIPS criteria of psychotic disorder or clinical risk for psychosis, and they were not included in further analyses.

After the exclusion criteria and inclusion criteria based on SIPS were applied, a total of 164 participants from the original 228 participants were included in the analyses. Our clinical high risk (CR) group consists of those who fulfilled modified criteria for the psychosis prodromal syndrome: specifically these require meeting all the other criteria of prodromal syndrome of SIPS save for the criterion of the recency of symptom onset. According to standard SIPS criteria for the prodromal syndrome, not only must a person have the necessary subthreshold psychotic symptoms, but their symptoms must have began recently (within the last year). We preferred to follow the approach of Yung and colleagues in including in our clinical risk group those subjects who had long-standing mild psychotic symptoms (Yung et al., 2007). A total of 62 familial risk, 20 clinical risk, 13 psychosis, and 69 control subjects were included in the analyses (Figure 1). There were 7 CR subjects who belonged also in the FR group but in the analyses they were included only in the CR group. All but 1 CR subject were at risk for psychosis because of attenuated psychotic symptoms and 1 because of genetic risk/functional deterioration. The demographic information of these groups is displayed in Table 1.

TABLE 1
Demographic data on research groups

	FR (*n* = 62)		*CR* (*n* = 20)		*Controls* (*n* = 69)		*Psychosis* (*n* = 13)[a]		*F or* χ^2	*p*
Age, years [*M* (*SD*)]	22.8	(0.7)	22.7	(0.9)	22.7	(0.8)	23.1	(0.8)	$F = 0.8$	.523
Gender, female [*N* (%)]	34	(54.8)	15	(75.0)	42	(60.9)	7	(53.8)	$\chi^2 = 2.8$	.427
FSIQ [*M* (*SD*)]	110.7	(19.4)	117.5	(23.7)	112.6	(17.9)	106.1	(16.7)	$F = 1.1$	.366
Handedness, right [*N* (%)]	54	(87.1)	20	(100)	65	(94.2)	13	(100)	$\chi^2 = 5.7$	.128
Education									$\chi^2 = 9.7$	.021
Elementary [*N* (%)]	26	(41.9)	8	(40.0)	20	(29.0)	9	(75.0)		
High-school [*N* (%)]	36	(58.1)	12	(60.0)	49	(71.0)	3	(25.0)		

Note. FR = familial risk for psychosis. CR = clinical risk for psychosis. FSIQ = estimated full-scale intelligence quotient based on Vocabulary and Matrix Reasoning from Wechsler Adult Intelligence Scale–Third Edition (WAIS–III). [a]one of the psychosis subjects did not provide information about education level.

Psychotropic medication and substance use

The field study in 2007–2009 also included the Structured Clinical Interview for DSM–IV disorders, SCID-I (First, Spitzer, Gibbon, & Williams, 1996), a questionnaire about health and use of medications, and a urine test to explore the possible use of drugs. Of all the participants, only 11 (6.7%) reported current use (past three months) of any psychopharmaceutical drug. Antipsychotics were used by 2 of the psychosis cases (15.4%) and 1 of the CR cases (5%). Antidepressants were used by 2 of the subjects with psychosis (15.4%) and 1 of the CR (5%) and one of the control cases (1.4%). Mood stabilizers were used by 1 psychosis and 1 CR case (7.7%, 5%, respectively). Other drugs (narcotics and sedatives) were used by 2 of the psychosis (15.4%), 2 of the FR (3.2%), 1 of the CR (5%), and 1 of the control cases (1.4%). Substance use disorder (SUD), as defined by any SUD according to the FHDR, SCID-I, or a positive urine drug test, was evident in 16 participants (5 FR, 3 CR, 5 psychosis, and 3 control subjects).

Neuropsychological assessment

Neuropsychological assessment of the field study in 2007–2009 consisted of 14 tests that were administered in a fixed order during a 90-minute session by psychologists and advanced medical students who were all trained to use these particular tests. In order to document the neuropsychological profile of subjects at high risk for psychosis, the test battery was designed to cover several relevant cognitive functions. Moreover, in the case of IQ and memory, both verbal and visual functioning were assessed. The assessed cognitive domains and tests with short descriptions are listed below:

Verbal and nonverbal intellectual ability

- Vocabulary from the Wechsler Adult Intelligence Scale–Third Edition, Finnish version (Wechsler, 1997) assesses word knowledge and ability to express word meanings.
- Matrix Reasoning from the Wechsler Adult Intelligence Scale–Third Edition (Wechsler, 1997) assesses analogical reasoning, perception of details, and spatial perception.

Learning and memory

- Logical Memory, Immediate and Delayed parts from Wechsler Memory Scale–Revised, Finnish version (Wechsler, 1987) is a test where two stories are read aloud to be remembered first immediately after the reading and again after 30 minutes.
- California Verbal Learning Test–Research Edition, Finnish version (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) is a verbal learning test where the subject is presented with a shopping list with 16 items to be learned and remembered across five trials and recalled again after 20 minutes.
- Paired Associates Learning, PAL (Sahakian et al., 1988) from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Boxes are displayed in different places on the screen and are opened in a randomized order. One or more boxes (up to eight) will contain a pattern to be remembered, along with its associated position.

Executive functioning/working memory

- Digit Span Backwards (Wechsler, 1997) is a test where numbers in increasing length (2 to 8) are read aloud and must be repeated in reverse order.
- Semantic Fluency (Benton & Hamsher, 1976) is a test where the subject is asked to name as many words as possible from categories (animals, fruits/berries, and vegetables) in three separate trials of 60 s.
- Spatial Working Memory, SWM (Sahakian et al., 1988) from CANTAB is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. It is a self-ordered task, which also assesses heuristic strategy.
- Stockings of Cambridge, SOC (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) from CANTAB is a spatial planning test where the subject is shown two displays containing three colored balls. The subject

must use the balls in one display to copy the pattern shown in other display.

Working memory/attention

- Digit Span Forwards (Wechsler, 1997) is a test where numbers in increasing length (2 to 9) are read aloud and must be repeated in exactly the same order as they were presented.
- Sternberg working memory (Sternberg, 1966) is a test where the subject is presented with sequences of letters in increasing numbers (3 to 6), and one letter is then probed. The intervals in which the letter is probed varies from 2 to 12 s.
- Rapid Visual Information Processing, RVP (Sahakian, Jones, Levy, Gray, & Warburton, 1989) from the CANTAB is a test of sustained attention. A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudorandom order, at the rate of 100 digits per minute. Subjects are requested to detect target sequences of digits (e.g., 2–4–6, 3–5–7, 4–6–8) and to register responses using the press pad.

Decision making/reflection impulsivity

- Information Sampling Task, IST (Clark, Robbins, Ersche, & Sahakian, 2006) from CANTAB impulsivity and decision making tests. The test is similar to the "Beads Test" for jumping to conclusions (Startup, Freeman, & Garety, 2008). The tendency to gather information before making a decision is evaluated with two conditions. First is the fixed win condition, in which the subject is awarded a fixed number of points for a correct decision regardless of the amount of information gathered (that is, boxes opened), and then the decreasing win condition, in which the number of points that can be won for a correct decision decreases for every new bit of information that is gathered.

Fine motor functioning

- Grooved Pegboard (Trites, 1989) is a test of dexterity where subject must place 25 pegs to the board as quickly as possible with the dominant hand and non-dominant hand separately. The pegs are grooved, so placing the pegs resembles putting a key to a lock.

One of the tests, the Sternberg working memory task, was administered during functional magnetic resonance imaging (fMRI) and was completed by approximately three quarters of participants ($n = 120$); here we present only the behavioral results as imaging analysis will be presented separately. Two of the tests, CVLT and IST, alternated randomly so that every other subject did the CVLT and the other IST. The reason for not doing these tests on everyone was time constraints due to the fact that participants were also interviewed and MRI-scanned during the same day. All the other 10 tests were administered to all of the participants.

Statistical analyses

Predictive Analytic Software, PASW Statistics 18.0 (SPSS Inc., PASW Statistics Base 18, Chicago, IL, USA, 2009) was used for statistical analyses. The demographic variables were compared between groups using chi-square tests for categorical variables and analysis of variance (ANOVA) for continuous variables. The raw scores of neurocognitive ability tests that were normally distributed were transformed to standard equivalents (z scores) using the means and standard deviations of the control group. Test scores of Information Sampling Task were omitted from the graph because it is more of a decision making than an ability test (optimal performance in IST lies between the lowest and the highest scores). The neurocognitive profile was created so that the 0-line represents the performance of the control group against which the other three groups are compared. ANOVA was used to assess the mean differences in cognitive variables between the four groups. Kruskal–Wallis tests were performed instead of F tests for four of the cognitive variables that were non-normally distributed. The post hoc analyses were conducted for statistically significant differences ($p < .05$) in the ANOVA analysis with Tukey HSD (honestly significant difference) method to investigate which groups differed from each other. The significance level was set to .05. Four test scores were regarded as outliers and were removed from the analyses (one each from the RVP, PAL, and Grooved Pegboard: dominant and nondominant hand) because they were substantially deviant. Additionally, if a participant had a condition that could affect the performance on the test of fine motor function (for example, recently had injured hand) the test score was eliminated from analyses. Substance use as a possible confounding factor was analyzed with ANOVA with subsamples of participants without any substance use disorder or a positive urine drug test ($n = 148$). To explore the effect of group ascertainment regarding those subjects who had both FR and CR, a secondary analyses was performed where such subjects were in the FR group instead of the CR group (in contrast to the primary analysis).

RESULTS

All of the groups were comparable regarding most demographic variables (Table 1): gender, handedness, estimated FSIQ, and age. The groups differed significantly only regarding education, controls being most educated, individuals with psychosis being least educated, and high risk groups falling in between.

Univariate ANOVA showed that groups differed statistically significantly in learning and memory (Logical Memory) and the fine motor function domain (Table 2). Post hoc analyses with a correction for multiple testing showed that the psychosis group performed significantly worse than controls in both the immediate and delayed parts of the verbal memory test: Logical Memory immediate part (mean = 18.38, 95% confidence interval, CI [13.0, 23.77]; mean = 24.74, 95% CI [23.15, 26.33]),

TABLE 2
Neurocognitive performance of research groups

Neurocognitive domain and test variables	*FR (n = 62)*	*CR (n = 20)*	*Controls (n = 69)*	*Psychosis (n = 13)*	*ANOVA*[a] *F*	*ANOVA*[a] *p*	*Post hoc comparisons with Tukey correction*[b]
Verbal and nonverbal intellectual ability							
Vocabulary: Total raw score [*M (SD)*]	44.6 (9.6)	47.9 (11.9)	45.0 (10.3)	42.2 (9.2)	0.93	.44	
Matrix Reasoning: Total raw score [*M (SD)*]	19.2 (3.4)	19.9 (4.2)	19.7 (3.1)	18.7 (3.2)	0.41	.60	
Learning and Memory							
Logical Memory: Immediate, total raw score [*M (SD)*]	22.8 (6.6)	24.3 (8.3)	24.7 (6.6)	18.4 (8.9)	3.1	.02	psych < ctrl*
Logical Memory: Delayed, total raw score [*M (SD)*]	20.7 (6.3)	22.8 (8.3)	22.5 (6.7)	16.7 (8.2)	2.8	.03	psych < ctrl*
CVLT: Total score, Trials 1–5[c] [*M (SD)*]	60.6 (9.1)	61.9 (7.6)	60.7 (8.2)	51.5 (12.7)	2.7	.05	
CVLT: Long delay recall [*M(SD)*]	13.0 (2.7)	12.6 (2.5)	13.3 (2.3)	10.5 (4.0)	2.5	.07	
PAL: Total errors [*Md (IQR)*]	3.0 (1.8–10.3)	2.5 (1.0–5.8)	3.0 (2.0–7.0)	4.5 (2.3–16.0)	2.7	.39	
Working memory/attention							
Digit Span: Span Forwards [*M(SD)*]	5.9 (0.9)	5.8 (0.9)	6.1 (1.0)	5.8 (0.6)	0.86	.46	
Sternberg Task: Total errors[d] [*Md (IQR)*]	6.0 (4.0–9.0)	8.0 (3.8–10.0)	6.0 (4.0–9.0)	8.0 (6.0–10.5)	0.38	.56	
RVP: A′ [*M(SD)*]	0.88 (0.05)	0.90 (0.06)	0.90 (0.05)	0.87 (0.04)	2.4	.08	
Fine motor function							
GP: Time (s) for dominant hand [*M (SD)*]	64.5 (8.0)	66.3 (10.2)	61.4 (7.8)	70.0 (9.6)	4.9	.003	psych > ctrl**
GP: Time (s) for nondominant hand [*Md (IQR)*]	66.5 (62.3–73.0)	69.5 (60.0–77.5)	65.0 (60.5–72.5)	81.5 (64.5–89.8)	5.1	.049	psych > CR*, FR*, ctrl*
Executive functioning/working memory							
Digit Span: Span Backwards [*M (SD)*]	4.8 (0.9)	4.7 (0.9)	5.1 (0.9)	4.5 (0.8)	2.0	.11	
SOC: Problems solved in min. moves [*M (SD)*]	9.7 (1.8)	9.7 (1.8)	10.2 (1.5)	9.7 (1.7)	1.6	.24	
Semantic Fluency: Total score [*M (SD)*]	53.6 (11.0)	53.7 (12.3)	54.6 (10.8)	46.5 (10.8)	1.9	.13	
SWM: Strategy [*M (SD)*]	29.3 (6.0)	29.3 (5.6)	28.5 (6.0)	32.1 (4.3)	1.4	.23	
SWM: Total between errors [*Md (IQR)*]	8.0 (2.8–20.0)	3.0 (1.0–16.5)	8.0 (2.0–16.5)	20.0 (5.0–24.5)	0.9	.25	
Decision making/reflection impulsivity							
IST: Mean no. opened: Fixed win condition[e] [*M (SD)*]	15.5 (5.6)	20.0 (4.4)	15.9 (5.4)	16.9 (7.9)	1.7	.20	
Mean no. opened: Decreasing win condition [*M (SD)*]	12.1 (4.8)	12.0 (4.8)	11.1 (4.5)	9.3 (3.6)	0.6	.56	

Note. Medians, interquartile ranges (IQRs), and Kruskal–Wallis test scores are used for four non-normally distributed cognitive test variables. FR = familial risk for psychosis; CR = clinical risk for psychosis; psych = psychosis group; ctrl = control group; CVLT = California Verbal Learning Test; PAL = Paired Associates Learning; GP = Grooved Pegboard; SWM = Spatial Working Memory; SOC = Stockings of Cambridge; RVP = Rapid Visual Information Processing; IST = Information Sampling Task.

[a]Univariate analysis of variance;

[b]Post hoc comparisons with a Tukey HSD (honestly significant difference) correction for multiple comparisons and comparing all four groups;

[c]psychosis ($n = 8$), CR ($n = 12$), familial risk ($n = 34$), controls ($n = 37$);

[d]psychosis ($n = 9$), CR ($n = 18$), familial risk ($n = 43$), controls ($n = 50$);

[e]psychosis ($n = 5$), CR ($n = 9$), familial risk ($n = 28$), controls ($n = 32$).

*$p < .05$. **$p < .01$.

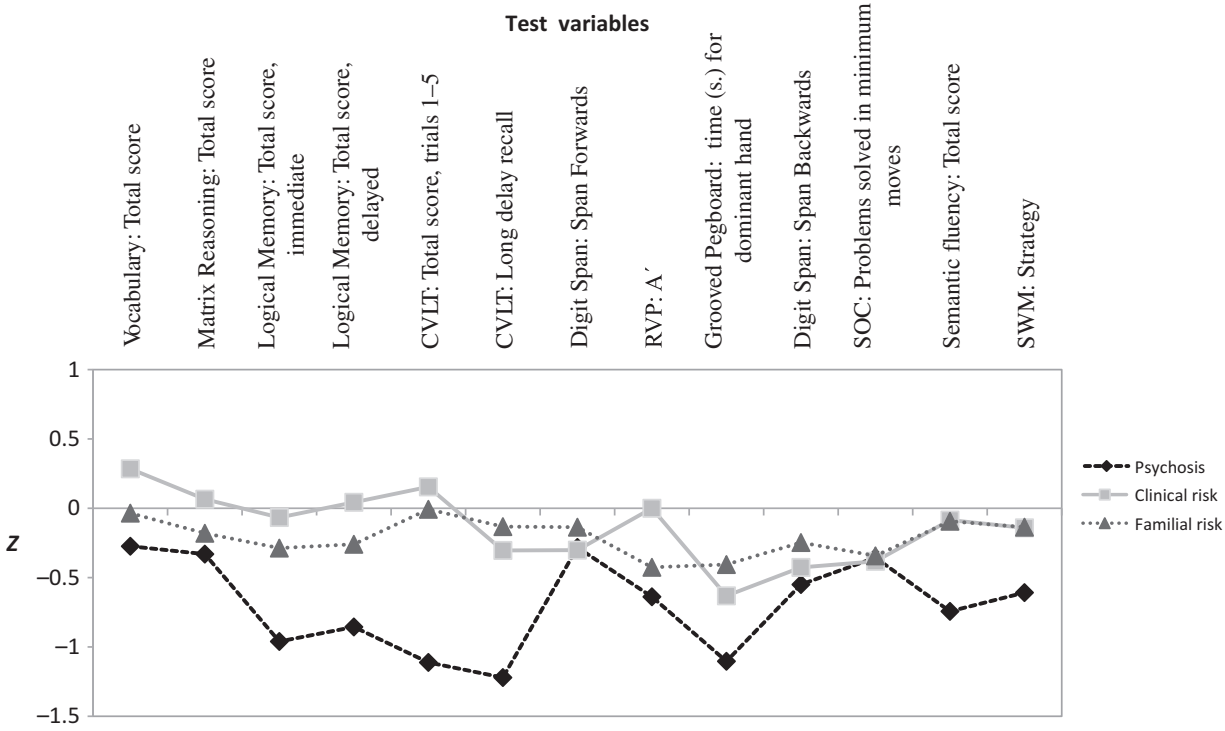

Figure 2. Neuropsychological profiles of familial risk, clinical risk, and psychosis group compared to controls. CVLT = California Verbal Learning Test; RVP = Rapid Visual Information Processing; SOC = Stockings of Cambridge; SWM = Spatial Working Memory.

$p = .017$, and delayed part (mean = 16.69, 95% CI [11.74, 21.65]; mean = 22.46, 95% CI [20.84, 24.08]), $p = .032$. Post hoc analyses showed that in fine motor function of the dominant hand the psychosis group was significantly slower than the control group (mean = 70.0, 95% CI [63.92, 76.08]; mean = 61.35, 95% CI [59.46, 63.25]), $p = .006$. Nondominant hand functioning was analyzed with Independent Samples Kruskal–Wallis tests due to nonnormal data distribution; this analysis showed that the psychosis group was slower than FR (median = 81.50, interquartile range, IQR [64.50, 89.75]; median = 66.50, IQR [62.25, 73.00]), $p = .027$; CR (median = 81.50, IQR [64.50, 89.75]; median = 69.50, IQR [60.00, 77.50]), $p = .022$; and the control group (median = 81.50, IQR [64.50, 89.75]; median = 65.00, IQR [62.50, 72.50]), $p = .022$. In post hoc analyses, with the one exception mentioned above, FR and CR groups did not differ significantly from the control or psychosis group in any domain. Also, FR and CR did not differ significantly from one another in any domain. Neuropsychological profiles of FR, CR, and psychosis group compared to controls are shown in Figure 2.

Separate univariate ANOVAs were performed for the same four groups excluding subjects with any substance use disorder or a positive urine test for drugs. The verbal memory function (Logical Memory total score immediate) no longer significantly differed among groups when subjects with evident substance use were removed from analyses. This was due to an apparent increase in scores in the psychosis group in Logical Memory when individuals with substance use were removed. No other changes were noteworthy in these analyses.

Univariate ANOVA and post hoc analyses, where those who had both FR and CR were included as FR instead of CR, showed that with the exception of one test, the results remained the same. Fine motor function of dominant hand differentiated the CR group from controls when those who also had FR were included in FR group (mean = 68.29, 95% CI [61.80, 74.77]; mean = 61.35, 95% CI [59.46, 63.25]), $p = .025$.

DISCUSSION

Two groups vulnerable to psychosis—familial and clinical risk—did not demonstrate significant neurocognitive impairments. Some of these results were more expected than others. For example, our finding that estimated FSIQ did not differentiate the CR group from controls is consistent with the conclusions in the review by Brewer et al. (2006) that states that general ability level as assessed by established batteries appears to remain relatively intact but more specific impairments are seen in subjects at high clinical risk for psychosis (Brewer et al., 2006). On the other hand, unlike M. Cannon et al. (2006) and two other earlier reports on subjects in their early twenties (Becker et al., 2010; Pukrop et al., 2006), and the NAPLS (North American Prodrome Longitudinal Study) report (Seidman et al., 2010), our study failed to

detect impairments in verbal fluency in high risk subjects with subthreshold symptoms. Also our finding that verbal fluency did not differentiate the FR group from controls contradicts the results from a study by Chen, Chen, and Lieh-Mah (2000) where nonpsychotic siblings of schizophrenia patients performed worse in semantic verbal fluency than controls (Chen et al., 2000). This discrepancy could perhaps arise from the notion that word categories used may have had different difficulty variation.

Our finding that familial and clinical risk subjects did not differ significantly in any domains in their neuropsychological profile is in contrast with the NAPLS results that indicated that profiles of these groups differed significantly (Seidman et al., 2010). However, we note that the majority of previous studies of clinical risk subjects, such as NAPLS, only include help-seeking individuals. Our study, being population based rather than clinic based, may have identified a less cognitively impaired group. In fact, our clinical high risk group had a somewhat higher estimated intelligence quotient than both the familial risk and control groups, although this difference was not significant. This could potentially mask other differences, since in some cases the higher the overall intelligence the better the other cognitive capabilities; however, this is not a straightforward matter. In addition, we recruited controls selected at random from the general population; such controls are likely to be more representative of the population than in previous studies but this approach may lead to less sensitivity to detect between-group differences. The Edinburgh high-risk study, which was not drawn from a clinic sample, found that symptomatic expression did not affect cognitive performance (O'Connor et al., 2009). However, this study did show that Spatial Working Memory and Stockings of Cambridge differentiated the family risk group from controls. Perhaps the strategy employed in the Edinburgh study of selecting only subjects with two close relatives with a history of psychosis resulted in a more cognitively impaired group than our sample, who were selected if they had one first-degree relative with psychosis.

It may be that, in order to find clear cognitive–behavioral changes in these vulnerable groups from the non-help-seeking population, high-demanding tasks or tasks that involve neural networks widely are needed. Some fMRI studies have shown that FR and schizophrenia subjects may differ significantly from controls in their neural activity even in situations where the behavioral results are the same, indicating that in affected subjects more neural effort may be needed in order to reach the same performance level (Johnson et al., 2006; Karlsgodt et al., 2007; Murray, Corlett, & Fletcher, 2010).

Not surprisingly, the psychosis group showed the most cognitive impairments compared to controls. Specifically, the psychosis group was impaired in verbal memory and fine motor function. Subjects with psychosis had also poorer fine motor function of nondominant hand than subjects with FR and CR. Interestingly, when subjects with evident problematic substance use were removed from the analyses, the verbal memory functions were no longer different among groups. This further highlights the point made in a recent study: The substance use history should be considered when cognitive functions are assessed in schizophrenia (Rodriguez-Jimenez et al., 2010). This same reasoning may apply in high risk studies.

Strengths and limitations

This study has several strengths. One is the use of a general population birth cohort study that allowed us to use data gathered earlier together with Finnish register data. That enabled us to create this research design where both familial and clinical high risk subjects for psychosis were assessed with an extensive neuropsychological battery. Using a one-year birth cohort from the general population is an advantage because it ensures that all groups of participants are matched with respect to age, genetic, and cultural background, thus limiting many potential sources of confounding. Another advantage of a population-based study is that it is relatively robust to selection biases. Our controls were not super-healthy controls in a sense that psychiatric disorders other than psychosis were allowed in our groups, largely because it is well established that high-risk groups may have psychiatric disorders (Korkeila et al., 2005; Svirskis et al., 2005). Another interesting feature of our study is that since we do not recruit from a clinic, our risk groups and psychosis patients are not the most severely ill/most severely high risk; thus our study may be more reflective of psychiatric phenotypes in the general population than many previous studies, and this confers both advantages and disadvantages.

A high attrition rate that contributed to small numbers in the final groups is one limitation in this study. Small group sizes limit the statistical power, potentially masking possible group differences. A second limitation is that, as yet, we do not know how many of our at-risk participants will develop psychosis. Rates of transition to psychosis are sensitive to many factors, including referral pathways to clinics, and, even within one clinic, transition rates and risk of psychosis may vary over time (Yung et al., 2007). It may be that structured interviews that are designed to diagnose those who are at high clinical risk for psychosis work best when applied to those populations who seek help or have recently deteriorated functionally: For a discussion of contemporary assessments of high risk for psychosis see Ruhrmann, Schultze-Lutter, and Klosterkötter (2010). Thirdly, one could argue that multiple comparison correction, Bonferroni adjustment, should have been used in the first phase of analyses (ANOVA). We chose, however, to deal with this problem of multiple comparisons by carefully choosing the cognitive tests so that they cover several separate cognitive functions. This way we were able to assess statistical differences without using Bonferroni correction, as suggested by Perneger (1998).

In summary, this study did not find significant neuropsychological impairments in two groups of well-matched, non-help-seeking young adults who were both

putatively high risk for psychosis, one through assumed genetic liability, and the other through apparent subsyndromal psychotic experiences. Furthermore, two high-risk groups did not differ significantly from another. Future studies should expand these results in larger but equally well-matched cohorts of individuals.

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