ORIGINAL CONTRIBUTION

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Impaired working speed and executive functions as frontal lobe dysfunctions in young first-degree relatives of schizophrenic patients

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■ **Abstract** The aim of the investigation was to detect neuropsychological markers, such as sustained and selective attention and executive functions, which contribute to the vulnerability to schizophrenia especially in young persons. Performance was assessed in 32 siblings and children of schizophrenic patients and 32 matched controls using Wisconsin Card Sorting Test, Colour-Word-Interference-Test, Trail Making Test, and d2-Concentration-Test. The first-degree relatives showed certain impairments on all four tests, in particular, slower times on all time-limited tests. These results suggest the need for more time when completing neuropsychological tasks involving selected and focused attention, as well as cognitive flexibility, as a possible indicator of genetic vulnerability to schizophrenia.

■ **Key words** schizophrenia – genetic vulnerability – attention – cognitive functions

Introduction

Schizophrenic disorder is characterized by clinical heterogeneity and certain neurobiological alterations. The world-wide constant prevalence of schizophrenia disease suggests an genetic influence. Especially high-risk-studies have shown a broad genetic component in the traits of schizophrenia [20, 23, 39, 43]. However, little is currently known about the nature of the transmission of inheritance. Furthermore, genetic predisposition may be clinically unexpressed. Thus, it is necessary to examine ill, stabilized or recovered patients as well as unaffected individuals who are at an increased genetic risk for schizophrenia disease. Cognitive processes are a directly expression of brain functions and especially their interactions. Thus, failured, prolonged, complicated or rigided ways of thinking in persons with a genetic risk reflect disturbed neuronal connections. Studying cognitive processes of unaffected first-degree relatives with a genetic risk for schizophrenia in comparison with healthy controls allows estimating the genetic impact of the disease on infomation-processing only if both groups were matched. Then they only differ in their genetic risk and we can lead back the differences to the impact of the genes. Various vulnerability models [41, 58] and certain neuropsychological indicators of attentional and cognitive abilities such as selective attention, cognitive flexibility, inhibitory control and naming skills were examined in detail among schizophrenic patients and risk persons [11, 14, 40]. Therefore, the idea of cognitive endophenotypes is an important approach in the research of genetic risk of schizophrenia since years [24, 52]. In research the Stroop Test (FWIT), the Trail Making Test (TMT), and the Wisconsin Card Sorting Test (WCST), have been used especially to assess executive or higher-order functions such as working memory, cognitive adjustment and maintenance of set. However, only few studies have applied the d2-Concentration-Test

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(d2) or the above-mentioned tests to a young population with a genetic risk.

Some studies have determined lower WCST-scores among schizophrenic patients. These have achieved a lower percentage of correct trials, fewer completed categories, and have made more preservative errors [16, 47]. Egan et al. [10] also determined impairments using the WCST and other tests among 193 unaffected siblings and even worse scores on these and other tests among 147 of their relatives who were patients. Further studies [12, 37, 38, 47, 48, 56] also indicate a genetic component regarding impairments among relatives of schizophrenic patients as compared to relatives of other patients with affective disorders and as compared to normal controls. Stratta et al. [53] showed lower WCST-scores among 92 schizophrenic patients, but not among 25 first-degree relatives. Other studies were also not able to detect any change in WCST-parameters among schizotypic persons or subjects with a genetic risk [28, 36]. Laurent et al. [33] showed deficits only in subgroups of relatives with higher rates of physical anhedonia and negative schizotypal symptoms. Therefore, the authors suggest that performance on the WCST is more likely a feature inherent to the disease process rather than an index of genetic susceptibility to the illness. WCST-deficits in schizotypic individuals [18, 42] support the hypothesis that executive function deficits may precede the onset of schizophrenia or indicate cognitive impairments in schizophrenic-spectrum syndromes.

Performance on the Stroop was also analyzed in detail among schizophrenic patients using various test versions. Impairments could be found repeatedly in patient groups. Nevertheless, some studies were not able to replicate these findings [33, 47]. In a review of 32 studies [19], inconsistent findings and the contribution of thought disorders and special components of the attention process to the Stroop-effect were emphasized. In genetic risk studies there are contradictory findings of poor performance among children, siblings and parents of schizophrenics [4, 9, 33, 47].

Impairments on the TMT, especially in the second part, could also often be determined in schizophrenic patients [33, 47, 57]. However, only a few studies were able to demonstrate lower scores among those at genetic risk [10, 33].

Some investigations showed impaired performance among schizophrenic patients or relatives on all of these tests: the Stroop, the TMT, and the WCST [13, 21, 27]. Only the investigations by Schreiber et al. [49] are known to have used the d2-Concentration-Test on schizophrenic patients and risk groups. On this test, patients, but not unaffected risks, performed more poorly (working speed and error rate) than did the controls. Furthermore, other tests have also shown reduced psychomotor speed and reaction time among schizophrenics [2, 49].

The findings described above suggest a subtle deficit in maintained and focused attention together with a subsequent impairment of stimulus discrimination among schizophrenics and schizotypical subjects. Due to these results, we assume these impairments principally to be an expression of the disease process, personality traits or symptomatology, such as schizoid, paranoid, extraversion, or anhedonia. Among subjects with a genetic risk for schizophrenia, cognitive dysfunctions have also been repeatedly determined [5, 32]. However, scores are inconsistent and display different impairment profiles [54]. Thus, it may be concluded that subgroups with various neurobiological and genetic profiles as well as certain symptomatology during the process of the disease can be distinguished and the vulnerable cognitive domains revealed.

The aim of this study (as part of an ongoing project called "Neurobiological and neuropsychological risk factors for schizophrenia"; [30]) is to consider the special cognitive abilities of working speed, inhibitory control, cognitive flexibility and executive functions, such as working memory, maintenance of set and naming skills using various tests among juvenile unaffected first-degree relatives of schizophrenic patients as compared to controls. Our hypothesis is that the genetic risk group of unaffected children and siblings of schizophrenics will score lower on the tests than will healthy controls. Based on frequently used tests and the results presented above, we selected the WCST, the TMT and the FWIT (Farbe-Wort-Interferenz-Test) as the German Version of the Stroop-Paradigm. A number of important studies [5, 11, 14, 32] refer to these test when assessing cognitive functioning and neuropsychological risk indicators in schizophrenic patients and persons at high risk, because these tests make demands on cognitive processes based in the frontal lobes, a brain area vulnerable to potential antecedents of schizophrenic disorder. All of these tests are supposed to have high effect sizes for test variation with a medium level of difficulty. Additionally, we used the d2-Test because it, in particular, makes demands on concentration and discrimination between similar stimuli under high time pressure in routine tasks.

Methods

Subjects

A total of 32 children and siblings of schizophrenic patients without any clinical manifestation of schizophrenic symptoms (mean age in years: 16.0;

males/females: 13/19) and 32 controls (mean age in years: 16.2; males/females: 13/19)—carefully matched for age (range from 12 to 21 years), sex and educational level—were examined. Additionally, in order to screen for the performance comparability of groups with respect to personal background data, the intellectual quotient was assessed using the Standard Progressive Matrices (SPM; [26] according to [37]). We assessed the educational level of probands and controls and also of parents of probands and controls as an indicator of their socio-economic status. Both groups did not differ significantly (Table 1). Demographic characteristics are summarized in Table 2. The high-risk subjects were drawn from a sample of schizophrenic in and outpatients of the Department of Psychiatry and Child- and Adolescent Psychiatry of the University of Jena and of two additional departments of psychiatry in the county of Jena. First-degree relatives of in and outpatients were asked for participation. The controls were recruited from all school types within the German School System. We also placed an ad in the local newspaper. People were asked to participate in a high-risk study conducted by the University of Jena as part of a neuropsychological study. Since recruitment was difficult we included both children and siblings of schizophrenic patients. Although siblings are a little more likely to be taken ill

at schizophrenia, the genetic risk on average is nearly the same for children and siblings [51]. We made up only one group for relatives, because the risk of schizophrenia is almost equal for both. The study was approved by the ethical commission of the University of Jena. All tests took place in the Department of Child and Adolescent Psychiatry in Jena. After a full explanation of the procedures to the subjects, written informed consent was obtained from the young persons and their parents.

■ Diagnostic screening and evaluation

Psychiatric status of both groups was determined according to the Schedule for Affective Disorders and Schizophrenia (SADS) or the Kiddie-SADS [8] by a board-certified psychiatrist or psychologist. First- or second-degree relatives of controls showing any schizophrenic symptoms were excluded, as were all probands suffering from internal or neurological disorders, schizotypical personality, affective or eating disorders, or diseases with a possible neurobiological basis, such as attentional deficit disorder or dyslexia. One subject in each group had an adjustment disorder, one had a minor depressive episode, two had social behavioral disorders without any symptoms of attentional deficit disorder, and one an enuresis. First-degree relatives showed no scores on SADS or were below threshold for diagnostic relevance. Inclusion criteria were an IQ of 70 or above according to SPM [31, 44] and an age between 12 and 21 years.

Table 1 Education level of probands and controls

	Probands with genetic risk	Controls
School type		
Lerning-Disabled School	1	1
Secondary School	15	14
Grammer School/Advanced Technical College/University	10/3	13/2
Technical College/Vocational School	3	2
Education level of the parents (always the highest qualification)		
Secondary School	3	1
Technical College/Vocational School	17	17
Advanced Technical College/University	12	14

Groups did not differ significantly

■ Neuropsychological evaluation

We used the (WCST; [22]) in order to examine the probands' executive functions such as working memory and maintenance of set as well as cognitive flexibility. The probands were asked to successively place 128 response cards, showing symbols drawn in different combinations of color, form, and number, under one of four stimulus cards. After ten consecutive correct trials, the criteria according to which the response cards were selected changed. The examiner provided information only on correct or incorrect choices and the probands had to find out by themselves according to what criteria the response cards were to be placed. We evaluated the percentage of correct trials (WCST/PCT), the percentage of perseverative errors (WCST/PPE), and the number of completed categories (WCST/NC).

The FWIT [1] as a version of the Stroop-Test was used to determine general alertness, naming skills and selectivity. At first the probands were asked to read aloud a list of color names printed in black, second to

Table 2 Demographic characteristics of probands

Demographic data	Subjects	
	Probands with genetic risk	Controls
Age (years)	16.0 ± 2.4	16.2 ± 2.0
Gender (male/female)	13/19	13/19
Intelligence (SPM-IQ) Non verbal IQ	101.6 ± 13.8	100.5 ± 9.7

Data of age and intelligence as mean values ± standard deviation
Groups did not differ significantly

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name the color of strokes, and third to name the color of different colored words. This run was repeated two times and the time required for reading was assessed. Finally, we calculated time needed (FWIT/A), naming skills (FWIT/N), selectivity of relevant information (FWIT/S), and number of errors on the interference task (FWIT/E).

The (TMT; [46]) provides information about psychomotoric speed, cognitive flexibility and working memory. Part A of the TMT requires the subjects to connect numbers in rising sequence. For Part B of the TMT, a line is drawn to connect alternating numbers and letters, starting with the number one, and then to the letter A, also in rising sequence. We determined time required for TMT/A and TMT/B as an indicator for working speed as well as cognitive flexibility using a ratio of TMT/A and TMT/B.

The d2-Concentration-Test (d2; [3]) provides information about the ability to discriminate between similar stimuli, measured by speed and accuracy of performance. The probands have to mark all "d"s that have two strokes within an array of 14 lines, with 20 s allowed per line. The probands must also discriminate between similar stimuli, because there are "d"s with one or more than two strokes, and "p"s with strokes. We counted the number of all scanned characters measuring the working speed (d2/GZ as the German expression for number of scanned characters). Furthermore, the ratio of incorrectly marked characters (d2/F as the German expression for error rate) to all scanned characters (d2/GZ) as an indicator of accuracy was assessed.

Results

The primary aim of the data analysis was to evaluate group differences for the parameters described above and to examine connections between the variables. Therefore, we tested our hypothesis that the genetic risk group of unaffected children and siblings of schizophrenics would perform more poorly on the tests than would healthy controls. Furthermore, we assumed that relatives of schizophrenics would show a wider pattern of impairments than would healthy controls. All statistical analysis were done using SPSS software (version 10.1).

The multivariate analysis of variance (MANOVA) showed significant differences between the group of children and siblings of schizophrenic patients and the controls for certain variables of performance, as well as a connection to age, intelligence and gender. In order to determine the normal distribution of parametric statistics for each variable, the score distributions of each group were examined using the Kolmogorov–Smirnov-test. Homogeneity of variance

of the groups was tested using the Levene Test. If there was no normal distribution, as was the case for the variables WCST/NC and TMT/F, then the non-parametric Mann–Whitney-U-test was used to evaluate group differences. Otherwise comparisons were made using the t-test. Mean scores (±standard deviation) are shown in Table 3. Correlations were determined using the non-parametric Spearman–Rank-test, with selected values shown in Table 4. Inhomogeneous variances arose in the variables WCST/NC, WCST/PCT, and FWIT/F. The level of significance was fixed at 0.05 for all tests.

Group differences

Compared to the controls, first-degree relatives of schizophrenic patients were significantly impaired in their performance on certain parts of all tests. For the WCST variables "percentage of correct trials" (PCT), "percentage of perseverative errors" (PPE), and "number of complete categories" (NCC), the analysis showed significantly worse results in the index group. The second finding of the three tests with time-limited demands, the FWIT, TMT, and d2-test, was that subjects with a genetic risk for schizophrenia worked at a significant slower rate as compared to the controls. Even though the variance of the significant results is greater in the high-risk group, these differences are not caused by extreme values. Statistical differences between the groups could not be detected for error rate on the TMT or on the d2, for cognitive control and flexibility or for naming skills on the FWIT (FWIT/N). However, first-degree relatives of schizophrenic patients produced significantly more mistakes on the interference task of the FWIT as compared to their controls.

Effects of age, intelligence and gender

These effects were taken into account in the analysis. As generally known, intelligence and speed on the FWIT, TMT, and d2, correct categorization on the WCST, as well as naming skills, improve with age for all probands. Intelligence correlated significantly with all measured performance except for selectivity and naming on the FWIT and for accuracy on the d2. With regard to gender effects (for a review, see [17, 55]) for all probands, females showed a significantly higher cognitive flexibility on the TMT/B. Among all probands and within the risk group, males achieved significantly higher accuracy when demands were placed on cognitive adjustment during the interference task of the FWIT. They scored significantly lower

Table 3 Comparison of neuropsychological data between high risk and control probands

Neuropsychological variable	Subjects		Comparisons
	Risk probands ($n = 32$)	Controls ($n = 32$)	p-values
WCST			
PCT, Percentage of correct trials	77.7 ± 10.5	84.0 ± 6.1	0.002+
PPE, Percentage of perseverative errors	9.8 ± 3.5	7.9 ± 2.8	0.010
NC, Number of complete categories	5.7 ± 0.8	6.0 ± 0.2	0.042*
FWIT			
A, Working speed	47.6 ± 8.0	52.2 ± 6.3	0.012
N, Naming skill	49.5 ± 7.0	49.0 ± 8.3	ns
S, Selectivity skill	54.7 ± 7.1	55.5 ± 8.4	ns
E, Number of errors during the interference task	14.9 ± 6.3	9.8 ± 5.1	0.000*
TMT			
A, Time to execute TMT part A	35.3 ± 10.6	27.8 ± 9.9	0.002
B, Time to execute TMT part B	83.0 ± 32.6	63.0 ± 18.6	0.002
E, Number of errors	0.47 ± 1.02	0.25 ± 0.57	ns*
A/B, Ratio of times of part A to B	0.462 ± 0.167	0.452 ± 0.121	ns
d2			
GZ, Number of treated signs	396.7 ± 97.7	448.9 ± 92.1	0.016
FGZ, Rate of errors to number of treated signs	3.6 ± 2.1	3.1 ± 2.9	ns

ns, Non-siginficant differences
Statistical analysis by *t*-test, not Bonferoni-corrected
*Non-parametric test (Mann–Whitney-*U*-test)
+p-values for inhomogeneous variances

Table 4 Selected correlations between the test variables for all probands ($n = 64$), shown as rho of Spearman-rank correlation

	WCST	FWIT		TMT	D2
	PCT	Errors	Action	A	GZ
WCST					
PCT, Percentage of correct trials		−0.354**	0.316*	−0.357**	−0.387**
FWIT					
Errors	−0.354**		−0.471**	0.347**	−0.331**
Action, Speed of a general alertness	0.316*	−0.471**		−0.416**	0.627**
TMT					
A, Time to execute TMT part A as an inverse indicator of working speed	−0.357**	0.347**	−0.416**		−0.463**
d2					
GZ, Number of treated signs as an indicator of working speed	0.387**	−0.331**	0.627**	−0.463**	

*Correlation two-sited significant at the level of 0.05
**Correlation two-sited significant at the level of 0.01

on naming skills than did the females. No gender effects were found in the control group.

■ Relationships between variables

The correlation between working speed and all time-limited tests (FWIT, TMT, d2) was highly significant, as was the correlation between speed and the PCT during the WCST. There is a positive connection between the accuracy of the d2 and the TMT. However, only the accuracy of the interference task on the FWIT correlated to parts of the WCST scores and the working speeds on the FWIT, TMT, and d2. While speed on the TMT is lower in the index group, there was no difference between the two groups regarding the ratio of the times required to complete the TMT/A and the TMT/B. Variable naming correlated only with general alertness on the FWIT. And selectivity on the FWIT did not correlate with any other performance variable.

Additionally, we did some factor analyses to see if different cognitive test variables could reflect the same cognitive function or a general vulnerability for schizophrenia. Surprisingly, after orthogonal rotation we found three factors explaining almost 60% of variance. But the other 4 of 7 components had "Ei-genwerte" between 0.55 and 0.97, so that we found almost as many factors as variables. After graphic representation, we are very cautious with an interpretation of the results of this factor analyses.

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Discussion

This study examined the hypothesis that children and siblings of patients with schizophrenia, without a schizophrenic-spectrum disorder, show a pattern of decreased attentional and cognitive performance when compared to controls. Several findings of this study can be emphasized.

First, subjects at risk for schizophrenia were slower on all three time-limited tests; the FWIT, TMT, and d2. These results suggest that young persons with a genetic risk need much more time to achieve the same accuracy as the controls during routine work on the d2 and the TMT/A. The correlations among working speeds for all time-limited tests indicate that these tests assess the same components of an attentional process and that this may reflect a general vulnerability. On the other hand, on tasks with no time structure or constraints high risks showed a lower ability to establish, maintain or adjust a required conceptual level during the WCST. This finding suggests impaired executive functions, working memory, vigilance and cognitive flexibility, which cannot be compensated by using more time, as compared to the controls. Furthermore, it is fair to assume that parameters of the prolonged and more complex tasks of the WCST measure different cognitive processes than do those of the time-limited tests. Nevertheless, there are correlations between WCST-scores and other scores, especially regarding working speed.

Second, gender effects are greater within the risk group. In this group, females showed a worse selectivity, but only by making more mistakes. In contrast, females performed significantly better than males on naming skills on the FWIT. These findings support the assumption of gender-specific vulnerability markers, in particular that males with a genetic risk show vulnerability in respect to naming skills [50].

Third, our findings regarding cognitive flexibility and naming skills on the FWIT are not reflected in the working speed for all time-limited tasks or in the intelligence of the probands. There is no correlation between these variables. However, there are significant correlations between the accuracy of the interference task on the FWIT with both the working speed for all time-limited tasks, as well as with WCST performance. Thus, both groups needed the same time to perform the interference task on the FWIT, but the high-risk probands made more mistakes. This is an indicator of impaired selectivity in distinguishing relevant from irrelevant stimuli. The results of the TMT test can be attributed to an impaired action speed but not to a lower ability of cognitive adjustment. Thus, the results do not allow a clear comparison of selectivity and naming performance in both

groups. Probably the FWIT subtests, with their demands on naming and cognitive adjustment, reflect other aspects of the attentional process as compared to other parts of the tests used.

These results in first-degree relatives of schizophrenic patients without schizotypical or affective symptoms only partly confirm prior studies. Some studies show no differences on the Stroop and the WCST [28, 33]. Only the scores on the WCST variables, "completed categories," "percentage of perceptual level response," and "perseverative errors," are repeatedly lower among the genetic risks as compared to the healthy controls, especially among high-risk probands affected by symptoms such as anhedonia or those that are schizotypical [33, 56]. TMT/B impairments could also be detected in groups with a genetic risk for schizophrenia [10, 33] suggesting a lower cognitive flexibility, again, particularly for subjects affected by schizoid or paranoid symptoms, extraversion or anhedonia [15, 34]. In contrast, we found lower working speeds on the TMT/A in the risk group, but not decreased selectivity on the ratios of the TMT subtests. However, we were able to confirm lower scores on the WCST among the risks without these special symptoms.

Some methodical issues must be discussed with respect to these findings. The sample size and power, the survey, the type of relatives and of control subjects may also account for the differences and the different results as compared to other studies. One factor relates to the motivation of the probands. Since they know themselves to be members of the index group it is possible that siblings or children of patients lack confidence in their own cognitive abilities and are, thus, less motivated than those in the control group. Nevertheless, abstract-logical intelligence is equal in both groups, although these scores are not influenced by time constraints. No ceiling or floor effects could be found so it may be assumed that all tests were sufficiently difficult. Furthermore, it is especially important to note that schizophrenia is etiologically heterogeneous. The higher standard deviation on almost all test variables relates to an inhomogeneous feature in the index group. Although subjects with a clinical diagnosis of a schizotypical personality disorder (SPD), affective or personality disorder were excluded, links to personality traits or other symptoms as described for our probands could also account for the lower scores in the risk group. We examined relatively small sample sizes. Therefore, an analysis of subgroups would not have been effective. In particular, a possible impact of the SPD dimensions could affect cognitive abilities, as suggested by the available studies of schizotypical persons. One could examine such effect by including a

third group, namely patients with schizophrenic disorder. We took in consideration to include also patients into our statistical analysis in order to look for a continuum in behavioral symptoms and cognitive performances. In our case, the patients group was too heterogenous. We did not succeed in matching three parallel groups of first-degree relatives, healthy controls and patients. Therefore, our focus lies on cognitive impairments of relatives of schizophrenic patients. Especially the recruitment of adolescent patients and much more of their relatives is a fussy issue in the research of neuropsychological indicators of cognitive abilities. Nevertheless, there is a need for further neuropsychological research to evaluate the impact of subtypes of schizophrenia on cognitive abilities. The discussion concerning the variability of risk groups is also reflected in our results with respect to the contrast of trait markers versus prodromali, the sensitivity of test versions and the specificity to schizophrenic disease [6, 7, 25, 29]. Furthermore, comparisons between the patients and their symptomatology during the course of the disease, and between subjects with genetic or symptomatical risks and controls may provide more insight into possible traits signaling vulnerability to schizophrenia. It is important to identify risk factors for schizophrenia as early as possible because of the poor prognoses for early-onset schizophrenia [35, 45]. The design of the present study did not allow the analysis of such a complex issue. Effects are currently being evaluated in order to determine patterns of cognitive vulnerability of risk subgroups. However, the results from our ongoing project did confirm a link to genetic influences, because both groups were matched for age, gender and intelligence. So the differences between probands and healthy controls are due to their relationship with schizophrenic patients, respectively to the genetic vulnerability of first-degree relatives. Our results demonstrate that attentional impairments as shown by the data of the FWIT, TMT, and d2 may be a trait indicator of the disease and so, too, may deficits of cognitive adjustment and executive functions as determined by the WCST. We were able to show that starting at a young age persons at risk work more slowly in general and not only on specific interference tasks. This suggests a more easily distracted working memory even among these young subjects. Therefore, our findings support the need for future studies based on the same and similar multiple tasks in order to gather more evidence in the search to identify subgroups of vulnerable subjects.

References

1. Bäumler G (1985) Farbe-Wort-Interferenz test (FWIT) nach JR Stroop. Göttingen: Hogrefe Verlag für Psychologie
2. Boucart M, Mobarek N, Cuervo C, Danion JM (1999) What is the nature of increased Stroop interference in schizophrenia? Acta Psychologica 101:3–25
3. Brickenkamp R (1994) Test d2—Aufmerksamkeits-Belastungs-Test. Hogrefe Verlag, Göttingen
4. Byrne M, Clafferty BA, Cosway R, Grant E, Hodges A, Whalley HC, Lawrie SM, Cunningham Owens DG, Johnstone E (2003) Neuropsychology, genetic liability, and psychotic symptoms in those at high risk of schizophrenia. J Abnormal Psychol 112:38–48
5. Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T (2000) Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophr Bull 26:379–393
6. Chen WJ, Faraone SV (2000) Sustained attention deficits as markers of genetic susceptibility to schizophrenia. Am J Med Genet 97:52–57
7. Davalos DB, Compagnon N, Heinlein S, Ross RG (2004) Neuropsychological deficits in children associated with increased familial risk for schizophrenia. Schizophr Res 67:123–130
8. Delmo C, Weiffenbach O, Gabriel M, Marchio E, Poustka F (1998) Kiddie–Sads-present and lifetime version (K-SADS-PL). Uni Frankfurt/M, Deutsche Forschungsversion
9. Dollfus S, Lombardo C, Benali K, Halpecq I, Abadie P, Marie RM, Brazo P (2002) Executive/attentional cognitive functions in schizophrenic patients and their parents: a preliminary study. Schizophr Res 53:93–99
10. Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, Bigelow L, Weinberger DR (2001) Relative risk for cognitive impairments in siblings of 11 patients with schizophrenia. Biol Psychiatry 50:98–107
11. Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, Adamo UH, Gottesman II (2000) Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: The New York High-Risk Project. Am J Psychiatry 157(9):1416–1422
12. Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT (2000) Neuropsychologic functioning among the nonpsychotic relatives of schizophrenic patients: the effect of genetic loading. Biol Psychiatry 48:120–126
13. Fitzgerald D, Lucas S, Redoblado MA, Winter V, Brennan J, Anderson J, Harris A (2004) Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. Aust New Zeal J Psychiatry 38:501–510
14. Freedman LR, Rock D, Roberts SA, Cornblatt BA, Erlenmeyer-Kimling L (1998) The New York High-Risk Project: attention, anhedonia and social outcome. Schizophr Res 30(1):1–9

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15. Gilvarry CM, Russell A, Hemsley D, Murray RM (2001) Neuropsychological performance and spectrum personality traits in the relatives of patients with schizophrenia and affective psychosis. Psychiatry Res 101(2):89–100

16. Glahn DC, Cannon DC, Gur RE, Ragland JD, Gur RC (2000) Working memory constrains abstraction in schizophrenia. Biol Psychiatry 47:34–42

17. Goldstein JM (1997) Sex differences in schizophrenia epidemiology, genetics and the brain. Int Rev Psychiatry 9(4):399–408

18. Gooding DC, Kwapil TR, Tallent KA (1999) Wisconsin Card Sorting Test deficits in schizotypic individuals. Schizophr Res 40(3):201–209

19. Grapperon J, Delage M (1999) Stroop test and schizophrenia. Encephale 25(1):50–58

20. Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 10(1):40–68

21. Hawkins KA, Addington J, Keefe RSE, Christensen B, Perkins DO, Zipurksya R, Woods SW, Miller TJ, Marquez E, Breier A, McGlashan TH (2004) Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res 67:115–12

22. Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G (1993) Wisconsin Card Sorting Test. Psychiatric Assessment Resources, Inc

23. Hodgekinson KA, Murphy J, O'Neill S, Brzustowicz L, Bassett AS (2001). Genetic counselling for schizophrenia in the era of molecular genetics. Can J Psychiatry 46(2):123–130

24. Hoff AL (2002) Is there a cognitive phenotype for schizophrenia: the nature and course of the disturbance in cognition? Curr Opin Psychiatry 15(1):43–48

25. Hoff AL, Kremen WS (2003) Neuropsychology in schizophrenia: an update. Curr Opin Psychiatry 16:149–155

26. Johnson JK, Tuulio-Henriksson A, Pirkola T, Huttunen MO, Lonnqvist J, Kaprio J, Cannon TD (2003) Do schizotypal symptoms mediate the relationship between genetic risk für schizophrenia and impaired neuropsychological performance in co-twins of schizophrenic patients? Biol Psychiatry 54(11):1200–1204

27. Johnson-Selfridge M, Zalewski C (2001) Moderator variables of executive functioning in schizophrenia: meta-analytic findings. Schizophr Bull 27(2):305–316

28. Kéri S, Kelemen O, Benedek G, Janka Z (2001) Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. Psychol Med 31(5):915–922

29. Kéri S, Janka Z (2004) Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. Acta Psychiatrica Scandinavica 110:83–91

30. Klemm S, Rzanny R, Riehemann S, Volz HP, Schmidt B, Gerhard UJ, Filz C, Schönberg A, Mentzel HJ, Kaiser WA, Blanz B (2001) Cerebral phosphate metabolism in first-degree relatives of schizophrenic patients. Am J Psychiatry 158:958–960

31. Kratzmeier H, Horn R (1988) Standard progressive matrices, manual. Beltz, Weinheim

32. Kremen WS, Seidman LS, Pepple JR (1994) Neuropsychological risk indicators for schizophrenia: a review of family studies. Schizophr Bull 20(1):103–119

33. Laurent A, Biloa-Tang M, Bougerol T, Duly D, Anchisi AM, Bosson JL, Pellat J, d'Amato T, Dalery J (2000) Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. Schizophr Res 46(2–3):269–283

34. Laurent A, Gilvarry C, Russell A, Murray R (2002) Personality dimension and neuropsychological performance in first-degree relatives of patients with schizophrenia and affective psychosis. Schizophr Res 55(3):239–248

35. Lay B, Blanz B, Hartmann M, Schmidt MH (2000) The psychosocial outcome of adolescent onset schizophrenia: a 12-years follow-up. Schizophr Bull 26(4):801–816

36. Lin CCH, Chen WJ, Yang HJ, Hsiao CK, Tien AY (2000) Performance on the Wisconsin Card Sorting Test among adolescents in Taiwan: norms, factorial structure, and relation to schizophrenia. J Clin Exp Neuropsychol 22:69–79

37. Liu Z, Zhao J, Tam WCC (2003) Attention and executive function impairments in unaffected siblings of patients with schizophrenia. Hong Kong J Psychiatry 13(2):8–11

38. Li-wen T, Zhi-kun Z, De-sen Y (2004) Negative symptoms and cognitive functions of the first-degree relatives of schizophrenics. Chin J Clin Psychol 12(2):188–191

39. Malhotra AK (2005) Current limitations and future prospects in genetics. Psychiatr Times 22(3):18–21

40. Michie PT, Kent A, Stienstra R, Castine R, Johnston J, Dedman K, Wichmann H, Box J, Rock D, Rutherford E, Jablensky A (2000) Phenotypic markers as risk factors in schizophrenia: neurocognitive functions. Aust New Zeal J Psychiatry 34:74–85

41. Nuechterlein KH, Dawson ME, Green MF (1994) Information-processing abnormalities as neuropsychological vulnerability indicators for schizophrenia. Acta Psychiatrica Scandinavica 384:71–79

42. Obiols JE, Serrano F, Barrantes N, Garcia Marimom M, Gras S, Bosch E, Caparros B, Carandell F (1997) Frontal dysfunction and psychosis proneness in CPT-linkend vulnerable adolescents. Pers Individual Diff 23(4):677–683

43. Picker J (2005) The role of genetic and environmental factors in the development of schizophrenia. Psychiatr Times 22(9):29–32

44. Raven J (1987) Manual for Ravens progressive matrices and vocabulary scales. Section 3. Standard progressive matrices. H.K. Lewis and Co. Ltd, London

45. Remschmidt (Hrsg) (2004) Schizophrene Erkrankungen im Kindes- und Jugendalter - Klinik, Ätiologie, Therapie und Rehabilitation. Stuttgart, Schattauer

46. Reitan RM (1992) Trail making test. Reitan Neuropsychology Laboratory, Arizona

47. Rybakowski JK, Borkowska A (2002) Eye movement and neuropsychological studies in first-degree relatives of schizophrenic patients. Schizophr Res 54(1–2):105–110

48. Saoud M, d'Amato T, Gutknecht C, Triboulet P, Bertaud JP, Marie-Cardine M, Daléry J, Rochet T (2000) Neuropsychological deficit in siblings discordant for schizophrenia. Schizophr Bull 26(4):893–902

49. Schreiber H, Rothmeier J, Becker W, Jurgens R, Born J, Stolz-Born G, Westphal KP, Kornhuber HH (1995) Comparative assessment of saccadic eye movements, psychomotor and cognitive performance in schizophrenics, their first-degree relatives and control subjects. Acta Psychiatrica Scandinavica 91(3):195–201

50. Schreiber H, Stolz-Born G, Heinrich H, Kornhuber HH (1992) Attention, cognition, and motor perseveration in adolescents at genetic risk for schizophrenia and control subjects. Psychiatry Res 44(2):125–140

51. Simon H, Cannistra SA, Huang E, Heller D, Shellito PC, Stern TA, Goldrosen J, Miller K (2005) Schizophrenia Report # 47. URL: www.well-connected.com

52. Sitskoorn MM, Aleman A, Ebisch SJH, Appels MCM, Kahn RS (2004). Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. Schizophr Res 71(2–3):285–295

53. Stratta P, Daneluzzo E, Mattei P, Bustini M, Casacchia M, Rossi A (1997). No deficit in Wisconsin Card Sorting Test performance of schizophrenic patients' first-degree relatives. Schizophr Res 26(2–3):147–151

54. Weickert TW, Goldberg TE, Bigelow LB (2000) Cognitive impairment in patients with schizophrenia with preserved and compromised intellect. Arch Gen Psychiatry 57:907–913

55. Weiser M, Reichenberg A, Rabinowitz J, Kaplan Z, Mark M, Nahon D, Davidson M (2000) Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. Schizophr Res 45(3):185–190

56. Wolf LE, Cornblatt BA, Roberts SA, Shapiro BM, Erlenmeyer-Kimling L (2002) Wisconsin Card Sorting deficits in the offspring of schizophrenics in the New York High-Risk Project. Schizophr Res 57(2–3):173

57. Wolwer W, Gabel W (2002) Impaired Trail-Making Test-B performance in patients with acute schizophrenia is related to inefficient sequencing of planning and acting. J Psychiatr Res 36(6):407

58. Zubin J, Spring B (1977) Vulnerability—a new view of schizophrenia. J Abnorm Psychol 86:103–126