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The Effect of Genetic Loading and Gender on Cognitive Functions of Unaffected Full Biological Siblings of Schizophrenia Patients

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ABSTRACT

Recent studies are giving consideration to the cognitive functions of schizophrenia which include deficits in abstraction, verbal memory, vigilance, language and executive functions. Only a small number of studies have addressed the effects of genetic loading and gender on cognitive performance in schizophrenia. In this article we shall be focusing on the following two aspects, firstly compare the performance of male and female full biological siblings of schizophrenic patients on cognitive tests and secondly, to find the influence of the genetic load on the performance of these tests.

This is a single point non-invasive study of non affected full biological siblings of patients with schizophrenia, involving administration of a battery of neuropsychological tests to assess the cognitive function in the siblings of schizophrenia patients.

On Wisconsin card sorting test (WCST), there was no significant difference between the male and the female siblings, except on percentage non-perseverative errors ($p=0.026$). On comparison on spatial working memory test (SWMT) and continuous performance test (CPT), there was no significant difference between males and females of sibling group.

The simplex group performed significantly better on all three tests as compared to the multiplex group.

In our study female sibling group performed significantly better than males on one parameter of WCST and one parameter of SWMT. Also, the siblings from multiplex families performed poorer as compared to siblings from simplex families on various

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parameters of WCST, CPT and SWMT.

Keywords : Male, female, simplex, multiplex, schizophrenia, cognition, Wisconsin card sorting test, continuous performance test, spatial working memory test, unaffected siblings

Introduction

Schizophrenia is arguably the most severe and disabling psychiatric disorder adversely affecting all the major domains of the patient's life-living independently and caring for themselves, working or attending school, fulfilling parental or other role obligations, and enjoying close relationships and rewarding leisure activities (1). In addition to the classically described 'positive' and 'negative' symptoms of Schizophrenia, recent studies are giving consideration to the cognitive functions of schizophrenia which include deficits in abstraction, verbal memory, vigilance, language and executive functions (2, 3, 4).

Although cognitive deficits have not yet been included in the diagnostic criteria of schizophrenia, they are one of the important core manifestations of this disorder and provide important diagnostic information, both in the phenotypic and prodromal phases. It has been proposed that abnormal cognitive functioning is a possible causal risk factor for psychosis, representing a third group of symptoms (5).

Owing to the large number of genetic and environmental variables which might lead to the development of Schizophrenia, researchers have found it difficult to identify those people who are currently asymptomatic and are at risk of developing schizophrenia at a later date. A possible way to find susceptibility genes for complex disorders may be using traits like variables associated with the disorder as phenotypes in genetic studies (6,7,8). For this reason, traits that can be observed both in patients and their relatives have come into focus. Because some relatives of patients carry genes for the illness although the illness is not expressing in them, the abnormal brain functioning that is often observed in them can be attributed to the effect that the illness genes have on the brain even in the absence of the full-blown illness (9). This effort to identify intermediate phenotypes, or endophenotypes, is driven by the idea that they involve the same biological pathways as the disorder but are closer to the relevant gene action than the categorical diagnoses,

thus adding power to genetic studies. Studies so far suggest that cognitive and psychophysiological aspects of brain function are more sensitive and reliable factors as endophenotypes for schizophrenia as compared to neruoanatomy or neurochemical findings (10). In several studies, cognitive deficits in relatives of schizophrenia patients have been found to parallel those observed in the patients, although to a milder degree. (11, 12).

Although it is known that female patients of schizophrenia tend to have better functioning and prognosis than males, previous studies have been unsatisfactory in eliciting a significant difference in the neuropsychological performance of the two sexes (13, 14).

Only a small number of studies have addressed the effects of genetic loading on cognitive performance. The majority suggest the expected negative relationship between genetic loading and aspects of neuropsychological abilities such as spatial delayed response task (15), delayed story recall, semantic verbal fluency, and inhibition response errors on a word completion test (16). Therefore the studies that examined associations with genetic loading indicated that both visual and verbal memory deficits hold particular promise as endophenotypes for the disorder.

This article is a part of a study conducted in the Department of Psychiatry, CSMMU, Lucknow, UP, India in which the performance of full biological siblings of schizophrenia patients was compared with that of unaffected controls (17). In this article we shall be focusing on the following two aspects, firstly comparing the performance of male and female full biological siblings of schizophrenic patients on cognitive tests and secondly, finding the influence of the genetic load on the performance of these tests.

Methods

This is a single point non-invasive study of nonaffected full biological siblings of patients with schizophrenia, involving administration of a battery of neuropsychological tests to assess the cognitive function in the sibling group. All subjects gave informed consent. The study was carried out from 1st September, 2005 to 1st August, 2006.

Sample consisted of nonaffected full biological siblings of patients with schizophrenia, both new and follow-up cases from district Lucknow, attending the outpatient section of the Department of Psychiatry, C.S.M Medical University on specified days of the week. Siblings

fulfilling the following selection criteria were taken up for the study:

The subjects were between the ages of 18 – 55 years and gave informed consent. The subject should have had at least 8 years of formal education, according to indian standards, and had no history of bipolar affective disorder, obsessive compulsive disorder, psychosis other than schizophrenia in the family (clinically assessed for available siblings and on the basis of history for those not available). They must have scored 3 or less on General Health Questionnaire, 12 item version (18).

Exclusion criteria for subjects included history of current or past psychiatric illness, history suggestive of significant physical disorder which can cause cognitive impairment such as seizures, cerebrovascular disorders, dementia, neurodegenerative disorders, systemic illness with known cerebral consequences, significant head injury, current or past history of any substance abuse or dependence, current use of medications known to impaire cognition like tricyclic antidepressants, antipsychotics, antiepileptics, benzodiazepines & lithium and physical problems that would render study measure difficult or impossible to administer or interpret e.g. blindness, hearing impairment, paralysis in upper limbs. The subjects in the control group were selected from the friends of the patients and healthy volunteers who gave an informed consent and fulfilled the following inclusion criteria: aged between 18-55years, should have had at least 8 years of formal education according to Indian Standards, and must have scored 3 or less on General Health Questionnaire, 12 item version. The subjects who had a past or present history of a psychiatric illness, medical disorders associated with cognitive impairment (seizures, cerebrovascular disorders, etc.) and head injury were excluded from the study as were those with present substance abuse or dependence, current use of medications impairing cognition (tricyclic antidepressants, antipsychotics, antiepileptics, benzodiazapines and lithium) and physical problems that would render study measure difficult or impossible to administer or interpret e.g. blindness, hearing impairment, paralysis in upper limbs. On specified days in adult Psychiatry O.P.D. C.S.M.M.U. patients (old and new) diagnosed as a case of Schizophrenia from district Lucknow were screened for the availability of the siblings. The diagnosis of schizophrenia was ascertained on detailed clinical evaluation using ICD-10 DCR. The available unaffected siblings were

ranked in the order of birth. One of the available siblings was randomly taken after applying the random number tables. Informed consent was taken and information regarding details of identification data, demographic profile, past history, negative history, family history, personal history and physical examination was obtained on the semistructured proforma. General Health Questionnaire, 12 item version (18) which is a measure in social science used for general mental well being with score more than 3 considered significant and warranting use of detailed assessment of an existing psychiatric illness, was used. The siblings were then assessed in detail on the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (19) (Wing et al., 1990) which is a standardized interview for ICD-10 diagnosis, to rule out any psychopathology or psychiatric illness.

Selection criteria were applied. If found eligible he/she was included in the study. If not eligible the next available sibling was randomly taken after applying the random number tables and assessment for participation in the study was done after taking the informed consent. The following computer based cognitive tests were administered by the investigator on the same day of inclusion so as to avoid loss at follow up or on a mutually convenient day if the subject was not willing to be tested on the same day or if there were more than one sibling included on the same day:

1. Wisconsin Card Sorting Test (WCST)

WCST (20,21) is a test of executive function requiring the ability to develop and maintain an appropriate problem solving strategy across changing stimulus conditions in order to achieve a future goal. It is a classical test for dorsolateral prefrontal cortex function (22). There are 4 cards employed in the test with each card having three stimulus parameters-colour, form and numbers. In the WCST, the subject is presented with a question card and the four stimulus cards and is asked to match question card to the stimulus cards but is not told which parameter to use (colour, form or number). However, he is told each time whether the response is right or wrong. After ten correct responses, the criterion for matching is changed without informing the patient. The subject is required to recognize the new criterion and change his responses accordingly. He/she is tested twice for each criteria. The responses and the scores on different parameters of this test are calculated and entered automatically. Intrascorer reliability coefficients for

WCST range from 0.828 to 1.000.

2. Continuous Performance Test (CPT)

Sustained attention, vigilance and impulse control is assessed by CPT (23, 24). The test requires a participant to respond to a specified target when it is presented spontaneously within a stream of interfering visual stimuli. The task involves monitoring a random series of geometrical figures.

Attention/vigilance involves maintaining a readiness to respond to a particular target stimulus and inhibiting responses to non-targets over a period of time. It requires one to distinguish targets from non-targets, an ability known as sensitivity. The results obtained are in terms of correct responses, wrong responses, missed responses and the reaction or response time. In the test, target stimulus is rare in frequency and presentation latency is brief. A total of 328 stimuli are presented, out of which 28 are for practice. Stimulus duration and inter stimulus latency are 50 milliseconds and 1000 milliseconds respectively.

3. Spatial Working Memory Test (SWMT)

Working memory is a type of explicit memory system involving short term registering of information. Working memory refers to the ability to maintain a limited amount of information for a brief time (seconds). Immediate memory is considered to be a component of working memory.

In SWMT (21), a test of memory for spatial locations, the subject views a brief presentation of black circle on computer screen and then is asked to point the location of circle after a delay of '0' second and '20' seconds, randomly. During the 20 seconds delay, the subject is engaged in a distraction task by asking to repeat continuously a 3 digits number, appearing on the screen, in reverse order.

The result in SWMT is obtained as number of correct responses and number of non-adjacent errors at 0 second and at 20 second delay respectively.

Results

In this study a total of 120 patients of schizophrenia were screened for the presence of siblings. No siblings were available for 25 of these patients. Out of the siblings that were available, 43 fulfilled the selection criteria but 7 did not complete the assessment. Therefore 36 siblings were included in the present study. The subjects in sibling group had a mean duration of education of 10.56 ± 7.72 years as compared to subjects of

control group who had a mean duration of education of

11.50. ± 8.20 years. 75% of subjects in sibling group were males as compared to 72.22% in the control group. The sibling and the control groups were statistically comparable to each other in context of sociodemographic variables such as age, gender, education, marital status, religion, place of domicile (urban or rural), occupation, family structure (joint or nuclear) and monthly family income (p values for all were >0.05).

Comparison of male and female siblings on computer based cognitive tests

The sibling group consisted of 27 males and 9 females. Table-1 shows the comparison of female and male siblings on the computer based cognitive tests (WCST, CPT& SWMT). On comparing the results of male and female siblings on WCST, it was found that there was no significant difference between males and females of sibling group on all the parameters except, percentage non-perseverative errors (p= 0.026). No significant difference was found between the male and female siblings in their performance on CPT (p>0.05). On comparison of results of SWMT, it was seen that there was no significant difference between males and females of sibling group in any of the parameters except, non-adjacent errors after 20 second delay in which the females performed significantly better(p= 0.014).

Comparison of siblings from simplex and multiplex families on computer based cognitive tests

The sibling group was divided on the basis of the number of patients of schizophrenia in their immediate family:

1) **Simplex family:** only one member in the family suffering from schizophrenia
2) **Multiplex family:** >1 member in the family suffering from schizophrenia

Most of the siblings belonged to simplex group (77.78%) i.e. one schizophrenia patient in the family and the rest (22.23%) belonged to multiplex group i.e. >1 schizophrenia patient per family.

Table 2 shows the comparison between siblings from simplex and multiplex group on various computer based cognitive tests. On comparison of their performance on WCST, it was seen that multiplex group performed significantly poorer on all the parameters except in trials administered, percentage perseverative responses and percentage perseverative errors. Although the above parameters did not show significant

Table 1: Comparison between male and female siblings on Computer based cognitive tests (WCST, CPT & SWMT)

Parameter	Females Mean ± S.D. (n = 9)	Males Mean ± S.D. (n = 27)	Comparison of Means
WCST			
Trial Administered	118.89 ± 11.86	125.26 + 6.92	t = 1.98, p = 0.056
% of total number of errors	34.33 ± 15.19	40.78 ± 11.96	t = 1.30, p = 0.200
% persevarative errors	14.89 ± 7.97	22.07 ± 8.06	t = 1.99, p = 0.055
% non-perseverative errors	19.22 ± 8.13	18.56 ± 6.30	t = 2.32, p = 0.026
% perseverative response	18.33 ± 9.48	25.22 ± 8.82	t = 0.25, p = 0.800
% conceptual level response	53.89 ± 21.30	46.56 ± 15.40	t = 1.12, p = 0.270
Categories completed	3.78 ± 2.27	3.22 ± 1.52	t = .83, p = 0.411
Trials to complete 1st category	29.44 ± 20.67	36.70 ± 29.84	t = .67, p = 0.505
CPT			
Wrong response	22.78 ± 24.39	24.04 ± 14.69	t = 0.18, p = 0.853
Missed response	15.89 ± 6.45	13.89 ± 11.26	t = 0.50, p = 0.618
Mean response time (in sec.)	2.87 ± .59	2.73 ± 1/06	t = 0.36, p = 0.718
SWMT Immediate response (zero second delay)			
Correct responses	23.00 ± 1.22	21.78 ± 1.69	t = 1.98, p = 0.055
Non-adjacent errors	0.56 ± 0.72	.67 ± 0.784	t = 0.37, p = 0.710
SWMT After 20 sec. delay			
Correct responses	20.67 ± 2.34	19.30 ± 2.10	t = 1.64, p = 0.110
Non-adjacent errors	0.33 ± 0.50	1.04 ± 0.75	t = 2.58, p = 0.014

Table 2: Comparison between siblings from simplex and multiplex families on WCST

Parameter	Simplex group Mean ± S.D. (n = 28)	Multiplex group Mean ± S.D. (n = 8)	Comparison of Means
WCST			
Trial Administered	122.43 ± 9.54	128.00 + 0.00	t = 1.63, p = 0.111
% of total number of errors	36.29 ± 12.12	49.25 ± 10.91	t = 2.72, p = 0.01
% persevarative errors	19.29 ± 8.79	23.75 ± 6.94	t = 1.32, p = 0.196
% non-perseverative errors	16.89 ± 5.32	25.13 ± 7.37	t = 3.53, p = 0.001
% perseverative response	22.43 ± 9.16	27.25 ± 9.69	t = 1.29, p = 0.203
% conceptual level response	52.46 ± 16.13	34.13 ± 12.23	t = 2.96, p = 0.005
Categories completed	3.93 ± 1.51	1.38 ± 0.52	t = 4.65, p = 0.000
Trials to complete 1st category	27.61 ± 14.76	60.38 ± 45.32	t = 3.34, p = 0.002
CPT			
Wrong response	21.25 ± 14.44	32.38 ± 23.85	t = -1.65, p = 0.108
Missed response	11.93 ± 7.92	23.00 ± 13.12	t = -2.99, p = 0.005
Mean response time (in sec.)	2.77 ± 1.02	2.75 ± 0.75	t = 0.06, p = 0.951
SWMT Immediate response (zero second delay)			
Correct responses	22.57 ± 1.29	20.38 ± 1.77	t = 3.91, p = 0.000
Non-adjacent errors	0.50 ± 0.67	1.13 ± 0.84	t = -2.15, p = 0.039
SWMT After 20 sec. delay			
Correct responses	19.64 ± 2.49	19.63 ± .74	t = .020, p = 0.984
Non-adjacent errors	0.71 ± 0.76	1.38 ± 0.52	t = -2.29, p = 0.028

difference but multiplex group performed poorer than simplex group even on these parameters. On comparison between simplex and multiplex group on CPT, it was seen that multiplex group significantly made more wrong responses (p=0.01) and significantly had more missed response (p=0.005). There was no significant difference between simplex and multiplex group in mean response time, however simplex group took more mean response time in seconds as compared to multiplex group. The siblings from multiplex group performed poorly on SWMT, as shown by the significantly less correct responses (p=0.000) and more non-adjacent errors (p=0.006) committed by them at zero second delay. The multiplex group made significantly more non-adjacent errors after 20 second delay (p=0.023) but no significant difference was observed in total correct responses after 20 second delay though multiplex group made less correct responses as compared to simplex group (p=0.984).

Discussion

The selection criteria were made stringent to minimize the confounding factors in evaluation of cognitive functions. Such confounding factors could have been extremes of age, psychiatric or significant physical disorders, significant substance use and use of medications associated with cognitive changes. Likewise a minimum level of cognitive functioning was ascertained by including only those siblings who were formally educated for more than 8 years. None of the siblings had taken any benzodiazepine on the day of cognitive assessment or five days prior to that, so that it was ensured that the sibling's psychomotor activity and reaction was not impaired and they were not sedated.

Low mean years of education of the subjects (sibling group: 10.56+2.13 years; control group: 11.50+2.59years) could be due to the fact that this hospital is a government hospital providing medical facilities mainly to people from low socioeconomic status. Also as a whole the literacy rates in India are lower than the western countries. The distribution of subjects according to religion, family structure, domicile occupation and monthly income was consistent with the patient population usually seen in the outpatient department of Department of Psychiatry, CSMMU, Lucknow, UP, India.

Mean age for the sibling group was 25.50+7.72 and this could be due to schizophrenia occurring at younger age group and the greater likelihood of siblings belonging to a similar age group

as the patients.

When females and males in the sibling group were compared among each other for the performance on various computer based cognitive tests by applying Independent t test, it revealed significant differences between the means of percentage non perseverative error where males committed significantly more errors as compared to females. Males also committed significantly more non adjacent errors after 20 second delay parameter in SWMT as compared to females. Considerations such as the later onset of psychosis in female patients and their superior prognosis may give the impression that female patients have cognitive performance superior to males. One neuropsychological study failed to support this conclusion and, without considering syndrome differences, found no sex differences (25). Egan et al., 2000 (26) found no differences between sexes in sibling or control group for any Continuous Performance Test measure. Bozikas et al., 2010 (27) assessed basic cognitive abilities: attention, working memory, abstraction, inhibition, fluency, verbal learning and memory, visual memory, visuospatial skills, and psychomotor speed on a battery of neuropsychological tests and found that the degree of cognitive impairment is the same for male and female schizophrenic patients. Further Goldstein et al., 1998 (28) studied sex differences in neuropsychological functions among patients with schizophrenia. In this study it was seen that male patients were significantly impaired across all functions in comparison with normal male subjects and on tests of attention, verbal memory, and executive functions in comparison with female patients though female patients performed significantly worse than female normal comparison subjects only on tests of attention, executive functions, visual memory, and motor functions. Hence it was here concluded that women with schizophrenia may be less vulnerable to particular cognitive deficits, especially those involving verbal processing, than schizophrenic men. Findings of our study cannot be generalized due to small sample size of female siblings as compared to males. Keeping in mind the mixed results of the previous studies, extensive future research is required to be conducted with a larger sample size to reach an unambiguous conclusion to this debate.

In the present study, siblings from multiplex family performed significantly poorly as compared to siblings from simplex families.

On Wisconsin Card Sorting Test (WCST) the sibling from multiplex

group performed significantly poorly as they made more total number of errors which implies that they had more difficulty in understanding the concept of the test as compared to siblings from simplex families (p=0.01). Among the errors, the siblings from multiplex families made significantly more number of non-perseverative errors (p=0.001). The siblings from multiplex families made significantly less number of conceptual responses (p<0.005) further supporting the notion that their understanding of the test was poorer than the siblings from simplex families. The siblings from multiplex group completed significantly more number of categories as compared to those from simplex group (p=0.000). The siblings from multiplex group also took significantly more trials to complete the first category (p=0.002) indicating that they initially had more problem in understanding the test than the siblings from simplex group.

In our study, on the test for attention, vigilance and concentration abilities – the Continuous Performance Test (CPT), the siblings from multiplex group made significantly more wrong responses i.e. the errors of commission (p=0.010), more missed response i.e. errors of omission (p=0.005) as compared to siblings from the simplex group. Findings in our study are supported by findings by Tsuang et al., 2006 (29) who compared the CPT performance of siblings from multiplex and simplex families and found that siblings from multiplex families exhibited worse performance on the degraded CPT and less proficiency in processing the perceptual load than those from simplex families. It can therefore be said that sustained attention along with perceptual load processing is more impaired in the siblings of schizophrenic patients with high familial loading and that this finding might be useful for future genetic dissection of schizophrenia.

Our findings after comparison between siblings from multiplex families and siblings from simplex families on SWMT are supported by reports from studies done earlier. Tuulio-Henriksson et al., 2003 (30) found an effect of familial loading (i.e., multiplex families versus simplex families) on a test of backward visual span. Faraone et al., 2000 (31) also showed greater impairment in individuals from multiplex versus simplex families on immediate and delayed story recall and immediate visual recall. Byrne et al., 2003 (32) showed a negative relationship between genetic liability (i.e., more than one affected first-degree relative > one affected first-and second-degree relative > affected second degree relatives) and delayed story recall, semantic verbal

fluency, and inhibition response errors on a word completion test.

The results of the study should be interpreted in view of the following limitations. Due to the constraints of a time bound study and because of the stringent selection criteria, the sample size was small and hence the results are subjected to Type II error. The small sample size makes it difficult to apply results to generalized population. The study is a cross-sectional study and to further clarify the state trait controversy longitudinal studies are needed. Cognitive functioning can depend on environmental (e.g. shared deviant rearing environment or gene-environmental interaction) and genetic factors. However, in the present study, any difference in the cognitive abilities is attributed to the genetic factors alone.

Despite the above limitations the present study has a few strengths when compared to many other studies in this area. Many confounding factors such as age, gender, significant physical illness, psychiatric conditions, substance use, and medication affecting cognition (e.g. benzodiazepines) were taken care of thus enabling the maximum attribution of the results to genetic sharing between the sibling and the index proband. The computerized version of these test were an added advantage as they ensured greater reliability, objectivity and standardization, less confrontational and formal approach. Moreover, it allowed the clinical assessors to have more time to focus on the patients rather than upon the presentation of the test material and data.

Our inclusion of only adult siblings as first degree relatives for assessment offers advantages (33) as compared to children at high risk study or including parents of those suffering from schizophrenia because having a parent with schizophrenia might interfere more with cognitive development than having a sibling with schizophrenia and adults may have already reached the peak age of risk for schizophrenia, having a parent with schizophrenia might interfere more with cognitive development than having a sibling with schizophrenia, age-linked stratification bias is reduced. Our siblings will not be affected by general decline in cognition seen with age which would have been the case if parents of those who are suffering from schizophrenia would have been included.

Conclusion

In the present study female sibling group performed significantly better than males on one parameter of WCST and one parameter of SWMT thus concluding that females may have better prognosis or greater resilience

to cognitive impairment than males. Also, the siblings from multiplex families perform poorer as compared to siblings from simplex families on various parameters of WCST, CPT and SWMT and hence support the finding of greater effect of genetic loading on cognition in siblings of schizophrenia patients. However these findings must be corroborated by further studies in future possibly with a greater sample size so that these findings could be applied to the general public.

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