

Comparison of Effect of Bipolar I Disorder on Neurocognitive Functions between Full Biological Siblings of Patients from Simplex and Multiplex Families

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Abstract

Background: Cognitive deficits seem to be more prevalent in relatives of patients with bipolar disorder type I compared to relatives of BD type II patients. Assessment of cognitive performance in siblings of bipolar disorder from simplex (only one known case of bipolar disorder in first degree relatives) and multiplex (more than one known case of bipolar disorder in first degree relatives) families may provide some light to investigate the biological vulnerability in bipolar disorder. There is limited data pertaining to studies on siblings of patients with bipolar disorder and especially on comparison of effect of Bipolar I Disorder on neurocognitive functions between full biological siblings of patients from simplex and multiplex Families. **Materials and Methods:** This is a prospective, teaching hospital based, single point non-invasive study of 29 unaffected full biological siblings of patients diagnosed (as per DSM-IV-TR) as bipolar disorder I (BD-I) from Simplex and Multiplex families. **Results:** The siblings belonging to the multiplex group performed poorly on most domains of the Wisconsin Card Sorting Test (WCST). Comparison of the performance of the siblings belonging to the multiplex sub-group to those of simplex sub-group on the various domains of the Continuous Performance Test (CPT) and Spatial Working Memory Test (SWMT) did not show statistically significant difference. **Conclusions:** The performance in WCST is significantly affected in siblings from multiplex families than in simplex ones.

Keywords: Bipolar Disorder Type 1, Cognitive Performance, Multiplex, Siblings, Simplex

1. Introduction

Bipolar disorder is a severe psychotic disorder with complex and multifactorial aetiology. Although clinical and epidemiological research of bipolar disorder has been a relatively neglected area in the past, this illness is receiving more and more attention. Healthy first-degree relatives of BD patients provide a powerful design to

investigate whether cognitive deficits in BD reflect state or trait markers^[1]. Cognitive deficits have been shown to be present in apparently healthy relatives of patients with bipolar disorder and thus they could be potential markers of familial vulnerability to bipolar disorder^[2,3].

The familial nature of mood disorders has been a widely observed phenomenon since antiquity. However, only in the last century have systematic studies been

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conducted that document the degree and nature of this familiarity as well as its genetic determinants.

The family study data clearly indicate that mood disorders are familial. However, such studies cannot distinguish whether genetic or environmental factors mediate the familial transmission. Families might share a variety of different environmental factors that could transmit the illness. Such factors might be behavioral but could also be shared exposure to infectious agents, toxins, or other brain insults. Twin studies provide the most powerful approach to separating genetic from environmental factors, or “nature” from “nurture.” Many strategies for twin studies have been used, but most commonly both Mono-Zygotic (MZ) and same-sex Di-Zygotic (DZ) twin pairs are identified in which one twin has a mood disorder.

Cognitive deficits seem to be more prevalent in relatives of patients with bipolar disorder type I compared to relatives of BD type II patients^[4]. Cognitive impairments hence may be considered as indicators of biological vulnerability. Also, the effect of genetic influence on phenotypes is an area which is yet to be explored fully. Therefore, assessment of cognitive performance in siblings of bipolar disorder from simplex (only one known case of bipolar disorder in first degree relatives) and multiplex (more than one known case of bipolar disorder in first degree relatives) families may provide some light to investigate the biological vulnerability in bipolar disorder. There is still paucity of data especially from this region. Further there is limited data pertaining to studies on siblings of patients with bipolar disorder and specially on comparison of effect of Bipolar I Disorder on neurocognitive functions between full biological siblings of patients from simplex and multiplex families; hence this study was planned to compare the effect of bipolar I disorder on Neurocognitive functions between full biological siblings of patients from simplex and multiplex families.

2. Materials and Methods

This is a prospective, teaching hospital based, single point non-invasive study of unaffected full biological siblings of patients with bipolar I disorder (BD-I) from Simplex and Multiplex families. Twenty-nine siblings of patients diagnosed (as per DSM-IV-TR) as bipolar disorder I (BD-I) from simplex and multiplex families who fulfilled the inclusion criteria were enrolled in the study.

2.1 Inclusion Criteria

1. Age 18-55 years
2. Informed consent
3. Minimum level of education: 8th standard
4. Bipolar I disorder in a full sibling (as per DSM-IV-TR criteria)
5. Three or less score on General Health Questionnaire, 12 item version^[5]

2.2 Exclusion Criteria

1. History of schizophrenia and psychosis in the first-degree relatives
2. History of current or past psychiatric illness
3. Current alcohol, psychoactive substance or drug abuse (except nicotine)
4. Current or past central nervous system disease or a medical illness with likely central nervous system manifestations (e.g. AIDS, SLE, Porphyrias), history of significant head injury
5. Physical problems that would render study measure difficult or impossible to administer or interpret e.g. blindness, hearing impairment
6. IQ less than 90
7. Current use of medications impairing cognition like benzodiazepines, antihistamines, TCA's, Opioid analgesics

Informed consent was taken and information regarding details of identification data, demographic profile, past history, family history, personal history, and physical examination was recorded on a semi structured proforma. General Health Questionnaire, 12 item version was applied and the sibling was then assessed in detail on the SCID-I to rule out any psychopathology or psychiatric illness.

Computer based cognitive tests: Wisconsin Card Sorting Test (WCST), Continuous Performance Test (CPT), Spatial Working Memory Test (SWMT) was administered by the investigator on the same day of inclusion. Four cases did not complete the workup and hence were excluded and 25 cases were available for analysis. Consent from all the cases was obtained. Ethical clearance was obtained from the institutional ethics committee. Statistical analysis of data was done using SPSS software (version 20). Mean, Standard deviation, 't' test for independent samples were employed for the analysis.

3. Results

Four of Twenty-nine siblings of patients diagnosed (DSM-IV-TR) as bipolar disorder I (BD-I) from simplex and multiplex families did not complete the workup and were excluded from the analysis; and hence 25 cases (18 simplex families, 8 multiplex families) were available for the analysis. In multiplex families there were more than one patient of bipolar affective disorder type I in their first-degree relatives. In simplex families there was only one known case of bipolar affective disorder type I.

Table 1, shows the comparison between the simplex and multiplex family group, based upon their performance on the WCST. The siblings belonging to the multiplex group performed poorly on most domains of the WCST but the results were statistically significant ($p < 0.05$) only on the % of total number of errors domain highlighting that siblings belonging to the multiplex group had significantly poorer understanding of the concept of the test.

Table 1. Comparison between siblings from simplex and multiplex families on Wisconsin Card Sorting Test (WCST)

Parameter	Simplex group (n=18) Mean ± S.D.	Multiplex group (n=7) Mean ± S.D.	Significance
Trial Administered	117.1 ± 16.9	128.0 ± 0	t=1.7; df=23 p=0.104
% of total number of errors	37.8 ± 16.8	53.0 ± 12.2	t=2.2; df=23 p=0.04**
% perseverative response	23.6 ± 18.0	34.7 ± 26.0	t=1.2; df=23 p=0.2
% perseverative errors	20.3 ± 13.3	29.9 ± 18.1	t=1.5; df=23 p=0.158
% non-perseverative errors	17.6 ± 7.1	23.1 ± 10.8	t=1.5; df=23 p=0.14
% conceptual level response	50.6 ± 22.8	31.6 ± 15.0	t=2.0; df=23 p=0.05
Categories completed	3.7 ± 2.1	2.4 ± 1.7	t=1.5; df=23 p=0.15
Trials to complete 1st category	29.0 ± 28.6	47.0 ± 56.0	t=1.1; df=23 p=0.3

**= statistically significant result, $p < 0.05$

Comparison of the performance of the siblings belonging to the multiplex group to those of simplex group on the various domains of the CPT is shown in (Table 2). The difference between the two groups was not statistically significant i.e. p value was greater than 0.05 in all the domains.

Table 2. Comparison between siblings from simplex and multiplex families on Continuous Performance Test (CPT)

Parameter	Simplex group (n=18) Mean ± S.D.	Multiplex group (n=7) Mean ± S.D.	Significance
Correct response	33.7 ± 8.5	30.3 ± 8.5	t=0.9; df=23 p=0.38
Wrong response	28.1 ± 27.0	21.1 ± 19.7	t=0.6; df=23 p=0.54
Missed response	10.3 ± 8.5	13.7 ± 8.5	t=0.9; df=23 p=0.4
Mean response time (in sec.)	0.4 ± 0.2	0.5 ± 0.2	t=0.4; df=23 p=0.67

**= statistically significant result, $p < 0.05$

Table 3, shows comparison between the simplex and multiplex group, based upon their performance on SWMT. Although, the simplex group performed better than the multiplex group on all the domains of the test, the results were not statistically significant in any of the domains i.e. p value was greater than 0.05 in all the domains.

4. Discussion

The present study was designed to compare the Neurocognitive functions in unaffected full biological siblings of patients with bipolar disorder type I from simplex and multiplex families.

Of the 25 siblings 7 (28%) belonged to multiplex families (more than one known case of bipolar disorder in first degree relatives) and the remaining 18 (72%) hence

Table 3. Comparison between siblings from simplex and multiplex families on Spatial Working Memory Test (SWMT)

Parameter	Simplex group (n=18) Mean \pm S.D.	Multiplex group (n=7) Mean \pm S.D.	Significance
At 0 second delay (immediate response)			
Correct responses	22.2 \pm 2.4	21.571 \pm 2.0	t=0.6 df=23 p=0.53
Non-adjacent errors	0.3 \pm 0.6	0.9 \pm 1.5	t=1.3 df=23 p=0.21
At 20 second delay			
Correct responses	19.3 \pm 3.1	17.143 \pm 2.795	t=1.61 df=23 p=0.12
Non-adjacent errors	1.00 \pm 1.3	1.7 \pm 1.6	t=1.17 df=23 p=0.26

**= statistically significant result, $p < 0.05$

belonged to simplex families. This division was done to see whether genetic loading has any effect on the cognitive dysfunction. Since there is increasing body of evidence regarding the polygenic inheritance of bipolar disorder^[6,7], individuals with higher number of first-degree relatives suffering from the disorder would be expected to have an increased risk of carrying the gene responsible for the disorder. It could hence be hypothesised that such individuals with higher genetic loading would have greater cognitive dysfunction. This study was limited because of the small sample size, (extreme values were affecting the mean due to small sample size) primarily because of time constraints; however, on the analysis of the data obtained by comparing the performance of siblings belonging to multiplex families vis-à-vis those belonging to simplex families, following trends were observed:

The subjects belonging to the multiplex families performed poorly on most domains of the WCST as compared to siblings of simplex families. However, due to small sample size results were statistically significant ($p=0.04$) in one domain only, namely, percentage of total number of errors. This implies that they had significant difficulty in understanding the concept of the test and hence had poorer abstract reasoning.

Other studies have also shown the relatives of patients with bipolar disorder to be having impairment in the executive functions^[8,9]. Familial resemblance for the WCST has been shown in families of bipolar patients^[10]. Healthy twins discordant for bipolar disorder showed significant deficits in executive functioning^[11]. Impairment in planning was found in first degree relatives of patients with bipolar disorder^[12].

Chowdhury, et al.^[13] in a review of cognitive dysfunctions in bipolar disorder, mentioned about an unpublished study conducted in their department that demonstrated a selective deficit in the executive control of working memory in first-degree relatives of bipolar probands, with intact verbal learning and memory.

However, studies done by Zalla, et al.^[14] and Keri et al.^[15] did not find any deficits in siblings of patients with bipolar disorder on WCST.

There was statistically no difference between siblings belonging to multiplex families and those to simplex families on all domains of CPT and SWMT.

The authors are yet to come across a study which specifically compares siblings belonging to simplex and multiplex families.

There is a need for replication of the findings in a larger prospective study based on a similar design. As this analysis was a cross-sectional study, one method would be to follow up a cohort of bipolar patients and their siblings and serially assess the neurocognitive functions at regular intervals.

Future studies are also required to investigate structural functional abnormalities in specific brain regions in high-risk cohorts and in familial bipolar disorder to further identify pre-existing neurobiological characteristics of prodromal Bipolar disorder.

5. Conclusions

Most of the research in bipolar disorder has concentrated on discovery of treatments and less on methods of prophylaxis. Attenuation or prevention of Bipolar Disorder has the potential to yield massive social and financial savings. Study of the relatives of bipolar patients represents one unique opportunity to the further understanding of early prodromal forms of bipolar disorder, which ultimately may lead to early identification and attenuation or prevention of the full disorder.

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