ORIGINAL ARTICLE

Executive Function and Attention Span in Euthymic Patients with Bipolar 1 Disorder

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SUMMARY

This is a cross sectional comparison study to assess executive function and attention span in euthymic patients with bipolar 1 disorder. It compares the performance of these two cognitive domains in 40 patients with bipolar 1 disorder to that of 40 healthy normal subjects using Trail Making (TMT), Digit Span (Forward and Backward) and Verbal Fluency (VF) tests. The association between demographic, clinical characteristics and performance in all tests were examined. Patients with bipolar illness showed significant impairment with moderate to large effect sizes (VF= 0.67, TMT A= 0.52, TMT B= 0.81, Digit Forward= 0.97, Digit backward= 1.10) in all tasks of executive and attention functioning. These impairments are observed in the absence of active mood symptoms while duration and severity of illness are not found to have an effect on both cognitive domains. Medications received by patients with bipolar disorder have significant association with performance on executive tasks. The results of this study add on to the existing global evidence of cognitive impairment in bipolar illness despite its cross cultural differences. Its presence in the absence of mania, depression or mixed episode indicates that cognitive impairment is stable even after symptoms recovery.

KEY WORDS:
Bipolar 1 disorder, Cognitive impairment, Executive function, Attention span

INTRODUCTION

Bipolar spectrum disorders affect approximately 2% of the general population[1] and contribute to significant morbidity and mortality from suicide. The illness is characterized by episodes of disturbed mood, sleep, behavior, perception and cognition. Bipolar I disorder is a psychiatric diagnosis that has recurrent manic, depressive or mixed episodes which are separated by periods of apparent recovery.

Significant cognitive impairment has been clearly demonstrated in patients with bipolar illness during acute and euthymic episodes [2,3]. It was clearly evident that every major domain of performance on neurocognitive tasks is disrupted which includes impairment in attention, memory and executive function [4,5].

The importance of cognition in bipolar illness lies on its effects on psychosocial and functional outcomes. Neuropsychological functioning has been postulated as a determinant of employment outcomes and up to 50% of bipolar patients experience significant social disabilities that may be related to persistent neurocognitive impairment[6].

A local hospital-based study on neurocognitive impairment in bipolar 1 disorder has shown up to 92% of patients having impaired short term memory and learning ability[7]. That impairment was observed in the absence of active mood symptoms using Rey Auditory Verbal Learning Test.

As such the aim of the present study is to determine patterns of attention and executive functions in euthymic patients with bipolar 1 disorder. It would be able to supplement the existing local data and have important implications in the planning of rehabilitation program for patients with bipolar disorder. In addition, screening for neurocognitive impairment would be implicated in all bipolar patients in future as a part of the clinical assessment because it would become the target for psychosocial treatment of bipolar illness.

MATERIALS AND METHODS

A cross sectional comparative design was used in the hospital-based study whereby 40 patients with bipolar 1 disorder constitute the case subjects while 40 normal healthy individuals were included in the comparison group. The case subjects were randomly selected from the attendance list in Psychiatric Clinic Universiti Kebangsaan Malaysia Medical Centre (UKMMC) (previously known as Hospital Universiti Kebangsaan Malaysia) within a six month period. Subjects in the comparison group were recruited from the hospital-based community which included healthy normal individuals working in the medical centre. They were an unmatched comparison group but the selected subjects would be most comparable to the case subjects in terms of the age range and level of education. Subjects' level of education was a relative measure of their premorbid intelligence which was one of the important confounding factors in the study. The age limit of all subjects was set between 18 to 60 years, to enable legal consent and to minimize the effect of normal aging process on the attention and executive function tests performance.

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They were literate and able to understand the national language (Bahasa Malaysia) and English.

The exclusion criteria for the case subjects of the study include overtly disturbed or aggressive patients, severe mental retardation or dementia, significant central nervous system diseases and history of head injury, comorbid psychiatric disorders and substance abuse or dependence and use of anticholinergic or benzodiazepine medication. As for the comparison group, an additional exclusion criterion would be those who have family history of psychiatric illness. The Ethic Research Committee of UKMMC granted permission to conduct the study after considering the associated ethical issues. On selection, subjects in both groups were assessed using Mini International Neuropsychiatric Interview[8] (MINI) diagnostic scale in order to generate DSM IV diagnosis of bipolar disorder and to rule out any psychiatric disorders in the comparison group. Following that, sociodemographic data was obtained and assessment for the symptomatology of the disorder was done on case subjects using Young Mania Rating Scale[9] (YMRS) and Hamilton Depression Rating Scale[10] (HAM-D). The first author administered all assessments.

Subsequently, all subjects underwent Trail Making[11] (TMT), Digit Span[12] (DS) and Verbal Fluency[13] (VF) tests to assess their attention and executive functions respectively. TMT provides a measure of motor speed and attention functions and is given in two parts, A and B. TMT part A is used to assess sustained attention and psychomotor speed while its part B measures attentional shifting and also psychomotor speed. Digit span is a subtest of WAIS-R[12] to measure selective attentional process and Verbal Fluency, dysfunction.

SPSS statistical software was used to analyse the data. Chi square, Independent t test and its non parametric equivalent were used in the analysis. P value of less than 0.05 was considered significant.

RESULTS

The demographic distribution of the respondents is tabulated in Table I. The median age for the case group is 37.5 and a median of 27.0 for the comparison group. Most respondents are within 18 to 39 years old where 55% of them are in the case group and 75% are in the comparison group. However, there is no significant difference for the age in both groups using a chi square test with a p value of 0.156.

About 52.5% represents the female gender in the case group and 47.5% of them are male. Majority of respondents in the comparison group are female (75%). The gender distribution shows significant difference between both case and control groups with the value of chi square = 4.38 and p value = 0.036 (Table I).

In marital status distribution, more than half of the respondents in both case and comparison groups are married and no significant difference between both groups with chi square = 0.82 and p value = 0.366. Majority of respondents in both groups are Malay, employed and have normal intelligence. Distributions of race and employment are statistically significant while there is no significant difference in intelligence between both groups (Table I).

The median age of onset of illness is 21 years and the mean duration of illness is 10.95 years with a standard deviation of +/- 9.04. All respondents in the bipolar group have no active manic or depressive symptoms as reflected by the median of YMRS and HAMD scores (Table II). The mean number of episodes of the illness is 3.83 times.

In categories of the treatment group, 27.5% of patients with bipolar illness receive mood stabilizer alone whereby seven out of 11 of them are on anticonvulsant. More than 50% respondents are on a combination of mood stabilizer and antipsychotic with 17 of them on atypical antipsychotic.

Table III shows the distribution of scores for Verbal fluency, Trail Making and Digit Span tests of all respondents from bipolar and comparison groups. Mean scores of all tests show significant difference between bipolar patients and normal healthy individuals with moderate to large effect size. The mean score of verbal fluency reflects the mean of total summation of words that respondents are able to produce across the three categories used i.e. animals, fruits and things. The difference is statistically significant with t value of -4.488, p value of 0.001 and moderate effect size of 0.67. It shows that patients with bipolar illness produce less total number of words across the three categories than normal healthy individuals.

For TMT parts A and B, the significant difference in mean scores between both groups signifies that bipolar patients take longer time to complete the tests than normal healthy people with moderate effect size of 0.52 for TMT part A and large effect size of 0.81 for TMT part B. In digit span test, large effect size of 0.97 measures the strength of the significant difference in mean scores of digit forward test between bipolar and normal healthy groups while effect size exceeding 1 is found in the mean score difference in digit backward test between both groups.

As some of the variables show large effect sizes in the analysis, further analysis was performed between clinical characteristics and scores for tests of attention and executive function. From the subgroup analysis, only the type of treatment received by patients and scores of verbal fluency differ significantly (Table IV) while other clinical characteristics were not found to have significant association with neuropsychological performances.

The relationship between types of medication received by respondents in bipolar group and categorical scores of verbal fluency test are presented in Table IV. In verbal fluency test, majority of the respondents who scored within normal limit fell in the group which received mood stabilizer, antipsychotic alone or a combination of both medications. The relationship is statistically significant with Fisher's exact value of 7.53 and p value of 0.029.

Table I: Association of demographic data between respondents in bipolar and normal groups using chi square test

Factors	Bipolar (n=40)		Normal (n=40)		X^2	p value
	No.	%	No.	%		
Age group (years old)						
18 – 39	22	55.0	30	75.0	3.72	0.156
40 – 49	11	27.5	7	17.5		
50 – 59	7	17.5	3	7.5		
Gender						
Male	19	47.5	10	25.0	4.38	0.036*
Female	21	52.5	30	75.0		
Ethnic group						
Malay	30	75.0	38	95.0	10.28	0.006*
Chinese	9	22.5	0	0.0		
Others	1	2.5	2	5.0		
Marital status						
Married	21	52.5	25	62.5	0.82	0.366
Single	19	47.5	15	37.5		
Premorbid intelligence						
Borderline	2	5.0	0	0.0	4.51	0.105
Dull Normal	6	15.0	2	5.0		
Normal	32	80.0	38	95.0		
Employment						
Employed	24	60.0	40	100.0	17.58#	0.001*
Unemployed	16	40.0	0	0.0		

Chi square with Yates correction, *p < 0.05

Table II: Clinical characteristics of respondents in bipolar group

Factors	Mean+/- s.d. / Median (IQR)	
Age of onset of illness (years old)	21(13)	
Young Mania Rating Scale (YMRS) score	2(4)	
Hamilton Depression Rating Scale (HAMD) score	0(0)	
Duration of illness (years)	10.95+/- 9.04	
Number of episodes	3.83+/- 3.07	
Medication	**No.**	**%**
1. Mood stabilizer (MS) only	11	27.5
2. MS and Antipsychotic (AP)	22	55.0
3. MS and Antidepressant (AD)	1	2.5
4. Antipsychotic (AP) only	6	15.0

s.d.=standard deviation, IQR=interquartile range

Table III: Comparison of scores of Verbal Fluency, Trail Making and Digit Span tests between bipolar and normal groups using independent t test and Cohen's effect size

Factors	Bipolar (n=40)	Normal (n=40)	t	P value	Effect size (Cohen's d)
	Mean +/- s.d.				
Verbal Fluency	44.85+/- 12.13	55.73+/- 9.31	-4.488	0.001*	0.67
TMT A (seconds)	46.53+/- 22.76	37.33+/- 9.99	2.341	0.023*	0.52
TMT B (seconds)	126.0+/- 62.37	88.13+/- 21.87	3.624	0.001*	0.81
Digit Forward	5.98+/- 1.08	7.13+/- 1.29	-4.344	0.001*	0.97
Digit Backward	3.60+/- 0.9	4.68+/- 1.05	-4.923	0.001*	1.10

s.d=standard deviation, TMT= Trail making test
*p< 0.05

Table IV: Association between groups of treatment and score of Verbal Fluency for patients with bipolar 1 disorder using Fisher's exact test

Factors	Medication								Fisher's exact	P value
	MS only		MS + AP		MS +AD		AP only			
	No.	%	No.	%	No.	%	No.	%		
Verbal Fluency Score										
Normal	11	100.0	21	95.5	0	0.0	5	83.3	7.53	0.029*
Abnormal	0	0.0	1	4.5	1	100.0	1	16.7		

MS=Mood stabilizer, AP= Antipsychotic, AD= Antidepressant
*p < 0.05

DISCUSSION

The present study demonstrates that bipolar patients in the absence of active mood symptoms have significant impairment in executive functioning and attention in comparison to normal healthy individuals with comparable age and premorbid intelligence. The findings of the study adds on to the existing cross cultural evidence on impaired cognitive functions in bipolar disorder as they replicate results of previousstudies conducted in Asia [14-16]. Despite using different subjects with wider range of age groups and different battery of neuropsychological tests, they concluded that executive and attentional functions of bipolar patients are compromised even when subjects are euthymic.

The magnitude of impairment in executive and attentional functions is indicated by the presence of medium to large effect sizes of performance in all neuropsychological tasks. Although tasks were all paper and pencil tests incorporated with clinical and assessment interviews, statistically significant deficits with such an effect size suggest cognitive deficits in patients with bipolar disorder have their clinical significance. This result was consistent with a past study as it used effect sizes in a meaningful way to describe the magnitude of the cognitive impairment [17]. However, the previous one differs from this study in that it also determined the proportions of patients with clinically significant cognitive impairment which gives greater impact on a target for therapeutic intervention.

The fact that both executive and attentional functions deficit in bipolar disorder persist in euthymic state gives an impression of its trait related nature rather than the result of the disease process. It has conflicting views because some studies found contrary results as they reported patients with more severe course of illness, greater number of episodes, hospitalizations and longer duration of illness which were associated with greater cognitive decline [18,19]. However, views supporting the trait dependent characteristic of bipolar cognitive deficit suggest that there is a role of genetic vulnerability as preliminary evidence has shown subtle impairment in neuropsychological performance in first degree relatives of patients with bipolar disorder [20,21]. It was reported that impairment in verbal learning and memory, response inhibition and information processing speed were seen reliably to have trait related nature[22]. In the present study, deficits in both cognitive domains in euthymic patients merely indicate that the impairment remained stable even after symptoms recovery but not trait related as the patients' premorbid data were unavailable.

With respect to demographic and clinical characteristics of patients with bipolar disorder,only medications received by the patients are associated significantly with the performance in verbal fluency and digit forward tests. The effects of psychotropic agents on cognitive function have been controversial as there was a mixture of negative and beneficial effects from previous studies. Some earlier studies have shown that lithium and anticonvulsants do not have a clinically significant impact on it [23-25] but a recent one reported a small but measurable adverse effect of lithium on memory[26]. Similarly, antipsychotics have been reported to cause both effects on executive function of patients with bipolar disorder[27-28]. In the present study, majority of the patients scored within normal limits in both tests although they performed poorly in comparison to normal healthy people. It suggests that both domains of executive functioning were fairly well restored in patients who received medications. Majority of them received anticonvulsants and atypical antipsychotic but this study is unable to differentiate whether mood stabilizer or antipsychotic has more significant effect on executive functioning of patients with bipolar disorder.

Two previous studies have found significant association between the use of antipsychotic and impaired executive functions in remitted patients with bipolar disorder but the results may be confounded by severity and course of illness and the presence of psychosis [29-30]. On the contrary, the present study found that majority of patients have fairly good performance in executive functions despite receiving antipsychotics potentially due to the fact that most of them belong to the younger age group and they are occupationally functioning. It is therefore worth to explore more on these associations and other factors such as the specific type and dosage of the medicines. These should be taken into account in order to clarify the relationship.

The present study does not report significant association between duration, severity of illness, numbers of episode and both cognitive domains in patients with bipolar disorder. The finding contrasts from a past study because majority of the patients recruited have a less severe form of bipolar illness than those selected in the earlier one[3]. In addition, duration and severity of illness are factors that have different measures of quantification in different studies which highlight the importance of having a standard measure to quantify those clinical factors in future.

A few issues need to be addressed in interpreting the findings in the study. Selection of the unmatched comparison group would have major impact on the results of the study. Bipolar patients recruited were not as well functioning as the control participants and they also differed in gender and ethnic groups. However their age group and pre morbid intelligence were comparable. Nonetheless these factors have not shown any significant effect on executive and attentional functions. It suggests that those factors do not account for differences in these two cognitive domains between the two groups and they may also be of a lesser value in influencing cognition in bipolar disorder. A small sample size may influence some of the findings and limits the use of more complex analysis to look at the predictive value of some of the associated factors on the cognitive domains. Results obtained from the tasks may be subjected to halo effect, as the rater is not blinded to the subjects in both groups. The information obtained tends to fit in with the observer preconception. Therefore, the use of independent rater would be a better choice to overcome this shortcoming in future studies.

In conclusion, the study is capable of discriminating impaired executive and attentional functions found in bipolar disorder from that in normal healthy individuals despite several limitations. The finding concludes that the presence of these deficits in bipolar disorder is universal despite cross-cultural difference between western and eastern populations. The

study also suggests that impaired executive and attentional functioning in bipolar illness is relatively stable after symptoms recovery. The result of the study adds on to the existing evidence worldwide that executive and attentional functions are impaired in bipolar disorder. As such, the data is important for local policy makers and rehabilitative specialists to design appropriate cognitive rehabilitation program that incorporates existing psychosocial management for bipolar disorder. It is also possibly helpful to include assessment of executive and attentional functions in a clinical setting to determine suitable rehabilitation programs for patients with bipolar disorder.

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