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Assessment of cognitive functions in bipolar-I disorder: A one-year naturalistic follow-up study

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Complete List of Authors:	Sagar, Rajesh; All India Institute of Medical Sciences, Psychiatry; All India Institute of Medical Sciences sahu, anamika; All India Institute of Medical Sciences, Psychiatry; anamika sahu, Psychiatry Pattanayak , Raman Deep; All India Institute of Medical Sciences, Psychiatry Chatterjee, Biswadip; All India Institute of Medical Sciences, Psychiatry
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Abstract:	Objective: Available cross-sectional studies have demonstrated cognitive impairments in Bipolar disorder-I (BD-I) during various phases. Very little is, however, known about the longitudinal course of these cognitive impairments across different phases. The purpose of the study was to explore the longitudinal pattern of changes in cognitive functioning in BD-I patients with currently depressed, manic and euthymic. Methods: A total of 180 individuals participated at baseline (131 subjects, 49 healthy controls). Subjects were aged 18-55 years, diagnosed as BD-I (using SCID-I) with formal education ≥5years, IQ > 80 with no psychiatric/medical comorbidity. All three patients groups and control group were assessed at baseline, three, six, nine and 12 months. Clinical assessments were carried out using 17-item Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS) and Brief Psychiatric Rating Scale. All groups were assessed for cognitive functions using Verbal Adult Intelligence Scale, Digit span, Postgraduate Institute Memory Scale, Colour Trails Test- trial 2, Stroop Test and Verbal working memory N-Back Test. Results: Compared to controls, all three patient groups performed poorly on all cognitive measures at baseline and follow-ups. However, manic patients showed improvement over time in delayed recall (p=<0.001), visual recognition (p=0.004) and executive functions (CTT-2-p=0.006; Stroop interference-p=0.002). Euthymic group improved on executive functions, especially interference task (p-<0.001) and working memory (p=0.001) whereas depressed patients improved on measures of executive functions (CTT-2-p=<0.001; Stroop interference- p=0.002). Conclusion: The study adds substantial information on longitudinal course of cognitive impairments in manic, depressed and euthymic individuals, with several clinical and research implications.

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Author

Rajesh Sagar, M.D.

rsagar29@gmail.com

Co-author(s):

Anamika Sahu, M.Phil, M.A.

cpanamika159@gmail.com

Dr Raman Deep Pattanayak, M.D., M.A.M.S..

drramandeep@gmail.com

Biswadip Chatterjee, MD

biswadip.c@gmail.com

Affiliation: Department(s) and institution(s)

Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India

Running Title: Cognitive functions in bipolar-I disorder

Corresponding Author:

Prof. Rajesh Sagar

Room No- 4089

Department of Psychiatry

All India Institute of Medical Sciences, New Delhi, India

Mail. Id- rsagar29@gmail.com

Phone no- 09810575310

Facsimile numbers. 01126589667

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ABSTRACT

Objective: Available cross-sectional studies have demonstrated cognitive impairments in Bipolar disorder-I (BD-I) during various phases. Very little is, however, known about the longitudinal course of these cognitive impairments across different phases. The purpose of the study was to explore the longitudinal pattern of changes in cognitive functioning in BD-I patients with currently depressed, manic and euthymic. **Methods**: A total of 180 individuals participated at baseline (131 subjects, 49 healthy controls). Subjects were aged 18-55 years, diagnosed as BD-I (using SCID-I) with formal education ≥5years, IQ > 80 with no psychiatric/medical comorbidity. All three patients groups and control group were assessed at baseline, three, six, nine and 12 months. Clinical assessments were carried out using 17-item Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS) and Brief Psychiatric Rating Scale. All groups were assessed for cognitive functions using Verbal Adult Intelligence Scale, Digit span, Postgraduate Institute Memory Scale, Colour Trails Test- trial 2, Stroop Test and Verbal working memory N-Back Test. **Results:** Compared to controls, all three patient groups performed poorly on all cognitive measures at baseline and follow-ups. However, manic patients showed improvement over time in delayed recall (p=<0.001), visual recognition (p=0.004) and executive functions (CTT-2-p=0.006; Stroop interference-p=0.002). Euthymic group improved on executive functions, especially interference task (p-<0.001) and working memory (p=0.001) whereas depressed patients improved on measures of executive functions (CTT-2-p=<0.001; Stroop interference-p=0.002). **Conclusion:** The study adds substantial information on longitudinal course of cognitive impairments in manic, depressed and euthymic individuals, with several clinical and research implications.

Keywords: Bipolar Disorder-I, Cognitive Functions, Longitudinal, India

INTRODUCTION

Bipolar-I disorder (BD-I) is an episodic, recurrent and often disabling illness[1] that involves alternate episodes of depression and mania. The prevalence of BD-I is estimated 0.6% in the continental United States whereas across 11 countries it falls in range of 0.0% to 0.6% [2]. In recent years, there have been increasing trend towards studies on cognitive functioning in bipolar-I and bipolar II disorder. A considerable amount of evidence in BD-I has confirmed impaired cognitive functions in the acute phase of illness and during remission of affective symptoms, namely euthymic state as well[3]. Cross sectional studies from Indian sub continent have also demonstrated a largely similar profile of cognitive deficits in patients with BD-I [4-7]. With regard to group comparisons, few cross-sectional studies have examined neuropsychological dysfunction among manic, depressed, and mixed-episode[8] or bipolar manic/hypomanic, depressed, and euthymic states[9,10]. These found impairments in attention, memory, information processing and learning functions in acute and remitted bipolar patients.

Additionally, despite the large number of cross-sectional studies, till date, only a few focal longitudinal studies have been conducted to assess the time course of cognitive functions in BD-I. No clear conclusion can be drawn from these few studies, with some studies reporting a decline in cognitive functions[11-13], few have found cognitive impairments to be stable over time[14-16] yet others have even reported progression in certain cognitive domains[17-19].

In addition to the inconclusive findings in existing few longitudinal studies, as pointed above, the available longitudinal studies have been centred on euthymic patient group only. In short, there has been no longitudinal study of cognitive functions across the different groups of BD-I i.e. patients currently depressed, manic and euthymic. Longitudinal studies in this direction are warranted. Further, studying cognitive performance in BD-I has clinical implications. It

has a detrimental impact upon adherence to therapeutic intervention or/and patient compliance and psychosocial functions [20].

Therefore, the present study was planned to evaluate the longitudinal course of cognitive functioning in a sample of clinically depressed, manic and stable euthymic patients with BD-I and compare these with healthy controls over a period of one year.

MATERIALS AND METHODS

Participants

After preliminary screening using selection criteria as outlined below, a total of 180 individuals participated in the study at baseline (T1), consisting of 131 subjects with BD-I currently either depressed, manic or euthymic, and healthy controls (n=49). Participants were recruited from the Outpatient Clinic of Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi, India. All subjects in patient group were between the ages of 18 and 55 years, either gender, fluent in Hindi language, with minimum of 5 years of formal education, IQ > 80 and were without a history of neurological disorders such as epilepsy and concussion with loss of consciousness. Diagnosis of BD-I (depressed, manic or in remission) was made for each participant using the Structured Clinical Interview for DSM-IV (SCID-I). In case of remitted patient group, patients were euthymic, for atleast 3 months, indicated by cut-off scores < 7 on the Hamilton Depression Rating Scale (HDRS-17-item) and < 6 on the Young Mania Rating Scale (YMRS). Patients were excluded if they had any co-morbid psychiatric illness or neurological disorder, current or lifetime diagnosis of substance dependence, intelligence quotient <80, history of electroconvulsive therapy in the past six months or a history of significant head injury involving loss of consciousness and refused to give consent for study.

The control group included healthy individuals aged between 18 and 55 years, either gender, absence of any axis I disorder based on SCID-CV, substance dependence other than nicotine, any medical or neurological disorder and family history of severe mental disorder (psychosis or major affective disorder) in first-degree relatives. Exclusion criteria for controls were same as that for patient group. Controls for study were non-biological relatives or attendants of patients, consenting staff members and individuals from the community.

Ethics approval was received from the Institutional Ethics Committee, AIIMS and written informed consent was taken from all subjects prior to participation.

Assessments

Patients group and controls were assessed at five time-points: at baseline assessments (T1), three months (T2), six month assessments (T3), nine months (T4) and twelve month assessment (T5). Following clinical and cognitive tests were administered:

Clinical assessment scales: SCID-I[21] was used for the clinical diagnosis of bipolar disorder at baseline (T1). At each interview (T1-T5), Brief Psychiatric Rating Scale-18items[22], HDRS-17[23] and YMRS-11 items[24] were administered to assess current psychopathology and severity of depressive and manic symptoms respectively.

Cognitive assessments: The cognitive assessment comprised of standardized clinical neuropsychological tests. All subjects completed these cognitive tests at each follow-up (T1-T5) visit.

(1) **Intelligence:**

***Verbal Adult Intelligence Scale[25]*:** This test was used to assess the verbal quotient at baseline. It is an Indian test and developed based on items of Weschler Adult Intelligence Scale-Revised, consists four subtests for general information, arithmetic, digit span and comprehension. Test–retest reliability over a period of 1–2 weeks was found to be between 0.87 and 0.98.

(2) **Attention:**

***Digit Span*[26]**: a subtest of Postgraduate Institute Memory Scale was used

(3) M**emory:**

***Postgraduate Institute Memory Scale*[26]:** It is a part of the PGI battery of brain dysfunction, and has been developed in India. The battery has been validated for use in the Hindi-speaking population. It consists of 10 sub-tests, of which three subtests were used in this study (immediate recall, delayed recall and visual recognition)

(4) **Executive Functions:**

***Colour Trails Test- Trial 2*[27]:** It designed as a culturally-fair analogue to the Trail Making Test (TMT). The CTT^{TM} uses numbered coloured circles and universal sign language symbols. Colour Trails 2 trial (Form A) was used for this study, where the respondent rapidly connects numbered circles in sequence, but alternates between pink and yellow colours. This test focuses on selective attention, mental flexibility, visual spatial skills and motor speed.

***Stroop Test –NIMHANS Neuropsychology Battery*[28]**: This test was designed to measure response inhibition in which a person can shift his or her perceptual set to conform to changing demands and inhibit usual response from interfering with the unusual one. The colour names “Blue”, “Green”, “Red” and “Yellow” are printed in the capital letters on a paper. Words are printed in 16 rows and 11 columns.

Verbal N Back Test[29]: The Verbal Working Memory N-Back Test is based on the theoretical premise that two variables, namely word length and phonemic similarity, can affect verbal working memory. In Back Task 1, the subject responds for consecutively repeated sounds and in Back Task 2, the subject responds if the sound is repeated after an intervening phoneme. The number of hits was used for study.

PROCEDURE

Subjects of all four groups i.e. depressed, manic, euthymic and controls, fulfilling the selection criteria were approached. After the informed consent, basic demographic information and clinical details has been taken. Further they were examined for cognitive functions at three monthly intervals over a period of 1 year, yielding a maximum of 5 assessments. Psychiatric interviews were conducted by a trained psychiatrist and cognitive tests were administered by a trained clinical psychologist. Each interview session took approximately 1 hour to complete and subjects were offered periodic breaks during testing. Modifications in treatment were done if required. During the follow-up period, none of the patients received any cognitive rehabilitation program.

STATISTICAL ANALYSIS

The data was analysed using Statistical Package for Social Sciences (SPSS) software, version 21.0 (SPSS, Chicago, IL, USA).Variables were first examined for normality using Shapiro–Wilk test. The groups were compared on demographic and clinical variables using either one-way analyses of variance (ANOVA) with Bonferroni post hoc corrections, or chi-square tests with Fisher's exact correction. After that, a general linear model of repeat measure analysis of variance was performed for normally distributed variables to assess the longitudinal course of neurocognitive tasks across five time period in all groups. Greenhouse Geisser correction was done when the assumption of sphericity has been violated (i.e. significant Mauchly's test). Further, Bonferroni post-hoc was used to see significant changes within groups. Group comparison for non normal distributed variables Kruskal-Wallis Test was used. Post hoc analysis was done with Mann-Whitney Test (Bonferroni correction, p=<0.008 used), to identify where the groups differed. Further, Friedman's Chi-Square Test was used to see changes across time point. When the Friedman Test p value obtained statistically significant,

post-hoc analysis with Wilcoxon signed-rank tests was conducted (Bonferroni correction p=<0.005 used) to examine where the differences actually occurred. A p-value of <0.05 was taken as significant. However, a higher emphasis was placed on a *p*-value <0.01 in view of the multiple tests.

RESULTS

A total of 213 subjects were screened and eligible patients recruited for study (Figure 1). The groups were assessed and compared at baseline (T1), three months follow-up assessments (T2-127), sixth month follow-up assessments (T3), ninth month follow up assessment (T-4) and twelve month assessment (T5).

A comparison of demographic and clinical characteristics of the study groups is presented in Table 1. As can be seen, patients and control subjects were similar in gender (p=0.360), occupation (p=0.475) and religion (p=0.711) but they differed in age (p=0.003), education (p=<0.001), marital status (p=<0.001), Locality (p=0.001) and socio-economic status (p=0.001). Specifically, healthy subjects were significantly younger than depressed (Bonferroni: p=0.008) and euthymic patients (Bonferroni: p=0.016) and had higher education as compared to patient groups. Majority of controls were single, belonged to middle socio-economic strata and resided in suburban area. At clinical parameters, the three patient groups did not differ in age at onset of the disorder, total duration of illness, number of total episodes including mania and depression and had similar number of manic episodes. However, a significant difference was found between all three patient groups on number of depressive episodes (p=<0.001). Post hoc analysis revealed that bipolar depressed patients had significantly greater number of depressive episodes then bipolar manic and euthymic patients. Additionally, significant group difference also can be seen on BPRS mean score (p=<0.001) where depressed and manic patients scored more than euthymic patients. As expected, manic

group had more score on YMRS while and depressed patients scored more on HDRS as compare to euthymic patients.

Table 2 shows the effects of groups (patients with depressed versus manic versus euthymic; inter-group effect), time (T1 versus T2, T3, T4, T5 assessments; intra group effect), and the group × time interaction in between groups. Within group difference over a period of time also shown with p value and Post-hoc analysis for BPRS. As seen from the table, there is a significant group effect (p=<0.001). In other words, inspite of one year time point, the group difference exist.

Table 3 shows the performance of patient groups and controls on the measures of attention (digit span) and memory (immediate recall, delayed recall and visual recognition). For analysis, a repeated measure ANOVA was used to see group effect, time effect and interaction between group and time. In addition, this table also depict improvement, deterioration or stable cognitive function within group across time point. For the attention, a main effect of group was observed (p=<0.001). In other words, despite having minimum symptoms of depression and mania across time, patients groups differed with controls on attention. Post hoc analysis revealed that depressed (p=<0.001), manic (p=<0.001) and euthymic patients (p=<0.001) performed poorly compared to controls. However, euthymic patients had little bit better attention as compared to depressed (p=0.031) and manic patients (p=0.035). There was also a little effect of time for attention, meant to slight improvement in attention with time, but no group × time interaction. Change within group across time point analysis shows that all groups were not significantly improved across time i.e. from T1 to T5. Regarding memory, a main effect of group was observed for immediate recall, for delayed recall and for visual recognition scores. There was also a main effect of time for all above variables that explain the changes occurred across time. Further, group × time interaction was

found for delayed recall and for visual recognition scores where the controls performance did not significantly change during time point assessments, but patients groups improved across time especially manic and euthymic group. When patient groups and controls were examined separately for within group timeline changes, manic and euthymic groups had higher scores on delayed recall and visual recognition at T5 and others than T1, indicating improvement over time. In depressed patients, only visual recognition is improved statistically (p=0.046).

Few cognitive variables, CTT-2, Stroop-interference, Verbal N-back-1 (Hits), Verbal N-back-2 (Hits), had non normal distribution, for which Kruskal-Wallis Test and Friedman Test were used to examine between group and within group differences over time respectively. Table 4 shows results of executive functions and working memory in patient groups and controls, in which group deference can be noticed at all measures. As seen from the table, there is a significant difference in the CTT2 task, with patients performing poorly compared to controls (p=<0.001). Post hoc analysis showed that on average, the patients took more time to complete the task as compared to controls. Additionally, manic patients at T1 and depressed patients at T3 and T4 performed poorly as compared to euthymic. The interference on stroop test was found more among patient groups (p=<0.001). All patients groups were found to have a significantly higher interference at T1 and T2. At T3, T4, and T5, especially, depressed and manic patients had higher interference as compared to controls. On both measures of N-Back test, statistically difference was found (P=<.001). Depressed, manic and euthymic patients made less hits than controls. However, euthymic patients performed better than manic patients at T1 and T2 of N-Back-1 and T2 to T5 of N-Back 2.

On within group timeline comparison of depressed group, there was a statistically significant difference in CTT-2 (P=<0.001), and Stroop-interference (p=0.002). Further post hoc analysis revealed that statistically significant reduction of time to complete CTT-2 task was noticed at six month and 12th months assessments as compare to baseline performance and in

stroop interference test, reduction of interference score was observed at six month and 12th months to baseline. In manic group, similar pattern was obtained. Euthymic patients performed significantly better on stroop interference (p=<0.001) and N-back-I tasks over time (p=0.001), especially at T5. As patient, controls also performed better on N-back-1 task.

DISCUSSION

To the best of our knowledge, this is one of the first studies from Indian subcontinent and internationally as well to attempt cognitive assessments over time across three different subgroups of BD-I. To date, very few studies in the existing literature have focused on the longitudinal course of cognitive functions in patients with BD-I, but those were primarily concerned with euthymic group. There are limited studies that have examined changes over time in the cognitive functions of typical asymptomatic and mildly symptomatic bipolar disorder patients[15,30]. Here, we present a one-year naturalistic follow-up study of cognitive functions in three groups of BD-I patients i.e. currently diagnosed with depressed, manic and euthymic. Compared to most of the earlier longitudinal studies, the study also included a relatively larger sample size in all three patient groups and a longer follow-up period with maximum five assessments over a year.

At the outset, two main findings regarding cognitive functions in BD-I patient groups emerged from the current study which need to be emphasized. First, patients with BD-I (depressed, manic and euthymic) remained cognitively impaired in all tested domains when compared to healthy controls at baseline, 3 month, 6 month, 9 month as well as 12 month assessments. Second, rather than deterioration in the cognitive functions, some cognitive functions improved over time and some remained stable as they were.

In regards to group differences in cognitive impairment at all time point measures, cognitive deficits were evident in sustained attention, memory and executive function regardless of

different clinical groups. Such results accord well with previous cross-sectional investigations that have demonstrated same trends of cognitive dysfunction in bipolar manic, depressed and euthymic patients[8-10]. The bipolar groups displayed worse performance on measures of verbal memory, executive function, speed of information processing, and dexterity than the control group[8]. Martínez-Arán et al.[10] have addressed several domains of cognitive function across different states of bipolar illness (30 depressed; 34 manic or hypomanic, 44 euthymic) and found dysfunction in verbal memory and frontal executive tasks in all three groups as compared to the comparison group. A recent study by Doruk et al.[9] assessed cognitive functions in 20 manic, 10 depressed and 21 euthymic bipolar I patients and have found impaired attention, memory and learning in manic and depressive patients than healthy controls and patients in remission. Additionally, these studies did not report any difference between patients in remission and healthy controls at all cognitive tasks.

Even with one year follow-up period, patients groups had persistent cognitive deficits as compared to controls. This finding has an agreement with previous existing researches that examined longitudinal course of cognitive function in euthymic groups either in midlife[15,17,31] or in elderly people[32,33], reported persistent or decline course of cognitive functions in Bipolar-I disorder. These deficits were found to be persisting even after improvement in symptoms of depression and mania. There is, however, a lack of study regarding longitudinal course of cognitive functions across BD-I patients currently having depression and mania. Bipolar depressed and manic patients were examined only baseline and reported cognitive deficits.

Further, the current study results also indicate improvement on few cognitive skills e.g. manic patients improved on delayed recall, visual recognition and executive function, euthymic patients improved on executive function, especially interference task and working memory[15,20,34] whereas depressed patients improved more on measures of executive

functions as compared to working memory and visual recognition. Additionally, some cognitive impairment remained stable over time i.e. attention, immediate recall and some extend working memory also. However, no evidence was found for deterioration in the cognitive functioning in any of the BD patient groups[16].

Improvement in cognitive functions might be affected by some confounding factors. For these factors, we need to look at a few methodological pitfalls of longitudinal studies e.g. practice effects and reduction in symptoms over time etc. Practice effects may mask cognitive improvement over time. We assessed patients at every three months over a year and we make sure about the exact time gap between two assessments. Additionally, we used more of verbal test instead of visual test. These patient groups experienced a reduction in symptoms especially on YMRS and HDRS over time. This possibility is less likely for depressed patients because they had subclinical symptoms of depression over time.

Furthermore, the findings of the study should be contextualized in terms of the strengths and limitations. The strength of the study includes assessing for the first time longitudinal course of cognitive function across manic, depressed, and euthymic patient among Indian population. There are few limitations of the current study that need to be mentioned and addressed in future studies. First, though this is the first study that included more number of manic and euthymic and depressed patients as compare to any of previous studies, however there is a need for still larger samples to ensure adequate statistical power for several of the analyses. Other important limitation of this study was that the patients were on psychotropic medication which could affect the cognition of patients. The possibility of persistent cognitive deficits in BD, atleast in some areas, is an issue of profound clinical and research interest that warrants further investigation.

To summarize, depressed, manic and euthymic BD patients were found to exhibit impairments in all cognitive domains when compared to healthy controls. The findings

do support that the presence of cognitive impairments may be an enduring feature of BD. Most importantly, the cognitive functions improved in some of domains over time while others remained stable in all patient groups. In addition, no evidence was found for deterioration in the cognitive functioning in any group. Future research needs to adopt sophisticated neuropsychological probes that are able to better define state and trait deficits and determine their functional impact in larger samples over a longitudinal course of time.

Conflict of Interest: The authors have no conflicts of interest to report.

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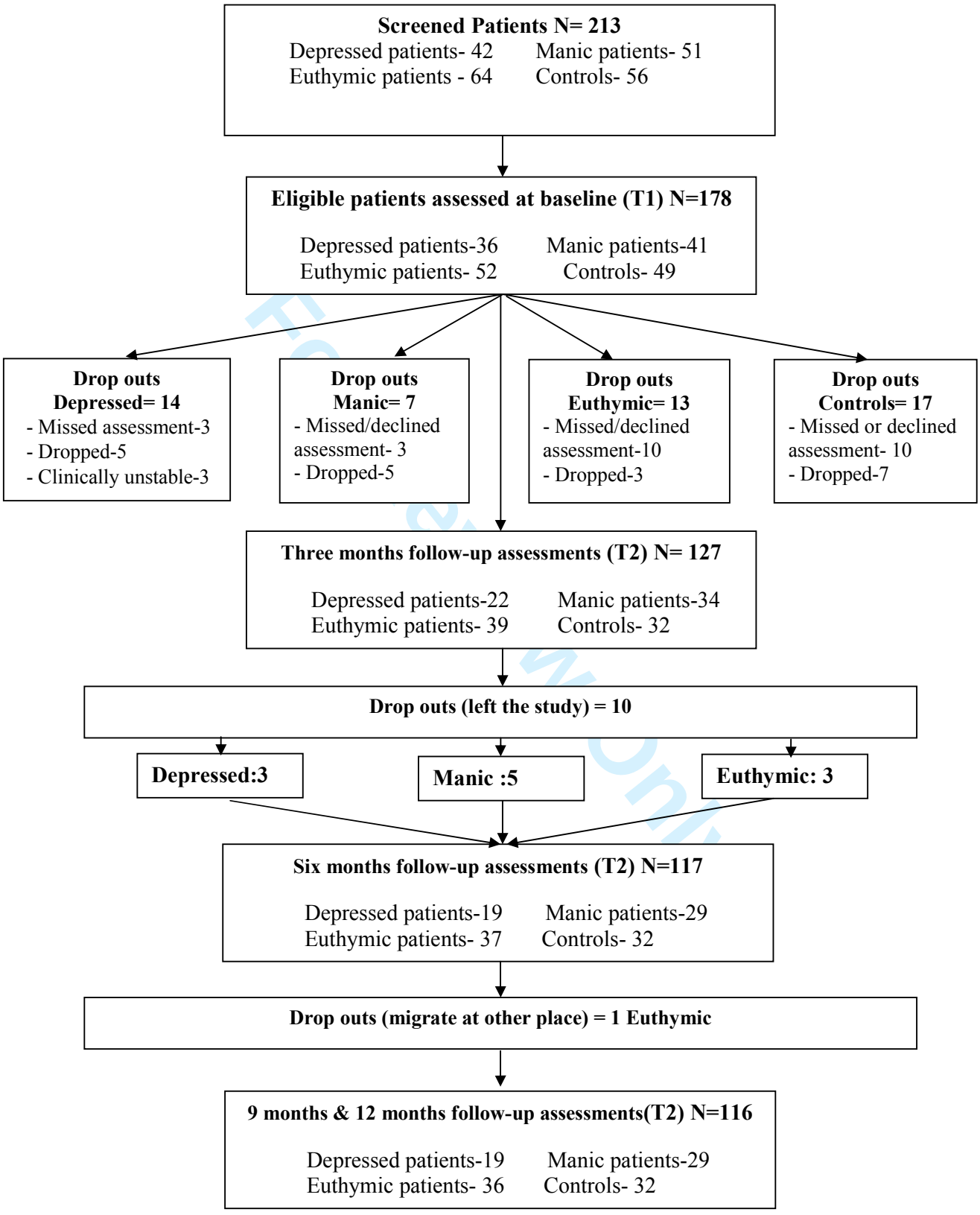

Figure 1: Flowchart to depict the sample at baseline and follow up assessments

Table 1: Socio-demographic and clinical variables: Group comparisons of the Bipolar- I disorder patient groups -depressed, manic, euthymic (n=84) and healthy controls (n=32)

Variables		BD-Depressed (n=19)	BD-Manic (n=29)	BD-Euthymic (n=36)	Controls (n=32)	p value	Post-hoc (Bonferroni)
Socio-demographic							
Age (years)[†]		37±12.97	31.72±12.30	34.72±13.02	26.53±2.69	0.003**[a]	C<D,E
Gender[‡]	Male	14 (15.56)	20 (31.11)	28 (31.11)	28 (31.11)	0.360[b]	
	Female	5 (19.23)	9 (34.62)	8 (30.77)	4 (15.38)		
Education[‡]	Matriculation	12 (63.16)	17 (58.63)	15 (41.67)	1 (3.13)	<0.001***[c]	
	Intermediate	4 (21.05)	4 (13.79)	10 (27.78)	6 (18.75)		
	≥Graduate	3 (15.79)	8 (27.59)	11 (30.56)	25 (78.13)		
Marital Status[‡]	Single	5 (9.62)	9 (17.31)	13 (25)	25 (48.08)	<0.001***[c]	
	Married	14 (22.58)	19 (30.65)	22 (35.48)	7 (11.29)		
	Divorced	0 (0)	1 (50)	1 (50)	0 (0)		
Occupation[‡]	Employed	9 (14.06)	16 (25)	21 (32.81)	18 (28.13)	0.475[b]	
	Unemployed	3 (42.86)	2 (28.57)	2 (28.57)	0 (0)		
	Others	7 (15.57)	11 (24.44)	13 (28.89)	14 (31.11)		
Religion[‡]	Hindu	18 (16.98)	27 (25.47)	31 (29.25)	30 (28.30)	0.711[c]	
	Others	1 (10)	2 (20)	5 (50)	2 (20)		
SES[‡]	Lower	11 (37.93)	8 (27.59)	9 (31.03)	1 (3.45)	0.001**[b]	
	Middle	8 (9.64)	19 (22.89)	27 (32.53)	29 (34.94)		
	High	0 (0)	0 (0)	2 (50)	2 (50)		
Locality[‡]	Suburban	12 (14.12)	20 (25.88)	22 (25.88)	31 (36.47)	0.001**[c]	
	Urban	7 (22.58)	9 (29.03)	14 (45.16)	1 (3.23)		
Verbal Intelligence (VQ)		91.367±7.08	94.13±8.07	89.34±7.85	102.28±13.58	<0.001***[a]	C>M,D,E
Clinical Variable							
Duration of illness (years) [†]		24.63±7.45	20.39±6.22	22.29±8.13		0.155 [a]	
Age of onset[†]		12.40±11.57	11.35±10.30	12.18±9.02		0.923 [a]	
Number of episodes[†]		8.63±7.79	4.72±3.86	5.39±5.01		0.49 [a]	
No of depressive episode[†]		4.58±3.71	1.86±1.12	1.97±1.24		<0.001***[a]	D>M,E
No of manic episode[†]		4.42±4.27	4.34±3.24	3.36±3.66		0.459 [a]	
BPRS[†]		29.63±5.53	26.28±6.24	20.08±2.84		<0.001***[a]	D.M>E
YMRS [≠]		0 (0-2)	20 (11-45)	0 (0-5)		-	-
HDRS [≠]		18 (8-32)	0 (0-6)	0 (0-6)		-	-

[†]Mean±SD; [‡]n (%); [≠] Median (min-max)
[a]F-test; [b]Chi square; [c] Fisher's exact test
** Significant value (p <0.01),***Significant value (p <0.001)
C= Controls; D=Depressed; M=Manic; E=Euthymic
T1-Baseline assessments, T2- Three months assessment, T3- Six month assessment, T4- Nine months assessment, T5- Twelve month assessment

Table 2: Clinical variables for depressed, manic and euthymic patients across various time points T1-T5 (n = 84)

Variables		BD-Depressed (n=19)	BD-Manic (n=29)	BD-Euthymic (n=36)	Group (G) effect (Post-hoc)	Time (T) effect	G × T interaction
BPRS[a]	T1	29.63±5.53	26.28±6.24	20.08±2.84	<0.001*** [c] D>E,M	<0.001***	<0.001***
	T2	21.90±3.18	19.38±2.71	19.64±2.57			
	T3	19.58±2.46	18.69±1.97	19.44±2.20			
	T4	22.32±4.79	19.35±2.87	18.83±1.94			
	T5	21.32±4.19	19.17±2.4	19±2.03			
P value [c] (Post-hoc-Bon)		<0.001*** (T1>T2,3,4,5)	<0.001*** (T1>T2,3,4,5)	0.067			
YMRS[b]	T1	0 (0-2)	20 (11-45)	0 (0-5)	<0.001*** (M>E,D)		
	T2	0 (0-17)	0 (0-5)	0 (0-6)	0.526		
	T3	0 (0-14)	0 (0-8)	0 (0-10)	0.891		
	T4	0 (0-31)	0 (0-21)	0 (0-2)	0.505		
	T5	0 (0-31)	0 (0-16)	0 (0-2)	0.309		
P value [d] (Post-hoc-Bon)[e]		0.873	<0.001*** T1>T2,3,4,5	0.436			
HDRS[b]	T1	18 (8-32)	0 (0-6)	0 (0-6)	<0.001*** (D>M,E)		
	T2	4 (0-16)	0 (0-18)	0 (0-12)	0.001** (D>E,M)		
	T3	4 (0-9)	0 (0-7)	0 (0-17)	0.002** (D>E,M)		
	T4	4 (0-18)	0 (0-16)	0 (0-13)	<0.001*** (D>E,M)		
	T5	4 (0-12)	0 (0-16)	0 (0-12)	<0.001*** D>E,M)		
P value [d] (Post-hoc-Bon)[e]		<0.001*** T1>T2,3,4,5	0.234	0.893	-		

[a]mean±SD
[b]median (min-max)
[c]Repeated Measures one way ANOVA
[d]Friedman Test
[e] Wilcoxon sign rank
** Significant value (p <0.01),***Significant value (p <0.001)
C= Controls; D=Depressed; M=Manic; E=Euthymic
T1-Baseline assessments, T2- Three months assessment, T3- Six month assessment, T4- Nine months assessment, T5- Twelve month assessment

Table 3: Cognitive performance across time periods in patient groups and control: Tests for attention and memory

Cognitive Domain (Measure)		BD-Depression (mean±SD)	BD-Manic (mean±SD)	BD-Euthymic (mean±SD)	Controls (mean±SD)	Group(G) effect (Post-hoc)	Time (T) effect	G × T interaction
Attention								
Digit span	T1	7.37±1.46	7.59±1.74	8.5±1.72	10.56±2.08	<0.001*** C>D,M, E E>D,M	0.024*	0.322
	T2	7.79±1.58	8±1.60	8.61±1.59	10.97±2.04			
	T3	7.68±1.16	7.59±2.04	8.58±1.59	11.06±1.97			
	T4	7.26±1.48	7.86±1.90	8.69±1.31	10.84±2.11			
	T5	7.90±1.24	7.66±1.82	8.69±1.75	10.84±2.11			
P value (Post-hoc-Bon)[a]		0.254	0.225	0.848	0.334			
Memory								
Immediate recall	T1	6±2.52	6.79±2.26	7.72±1.91	10.13±1.19	<0.001*** C>D,M, E E>D	<0.001***	0.313
	T2	7.58±2.39	7.55±1.77	7.97±2.08	10.63±1.19			
	T3	7.05±1.08	7.28±2.37	8.03±1.89	10.75±1.19			
	T4	7.21±2.94	7.79±2.14	8.06±2.06	10.69±1.18			
	T5	6.79±1.62	8.44±1.59	7.52±2.06	10.69±1.18			
P value (Post-hoc-Bon)[a]		0.091	0.681	0.157	<0.001*** (T1<T3,4,5,2)			
Delayed recall	T1	6.32±1.95	6.41±2.23	7.5±1.94	9.13±.98	<0.001*** C>D,M, E E>D	<0.001***	0.004**
	T2	6.90±2.08	7.69±2.00	7.61±2.05	9.16±.85			
	T3	7.16±1.43	7.28±2.43	7.78±1.81	9.19±.82			
	T4	6.95±1.62	8.06±1.41	8.17±1.79	9.06±.80			
	T5	6.84±1.83	8±1.93	8.36±1.53	9.06±.80			
P value (Post-hoc-Bon)[a]		0.530	<0.001*** (T1<T5,T4,T2)	0.043 *	0.601			
Visual Recognition	T1	6.87±2.20	6.09±2.36	7.8±2.03	9.34±.56	<0.001*** C>D,M, E E>M,D	<0.001**	0.037*
	T2	7.84±1.34	6.90±2.50	8.5±1.12	9.48±.65			
	T3	7.63±1.47	7.35±2.22	8.18±1.78	9.48±.69			
	T4	7.79±1.59	7.53±2.11	8.57±1.31	9.47±.76			
	T5	8.21±1.23	7.67±1.92	8.93±1.07	9.47±.76			
P value (Post-hoc-Bon)[a]		0.046*	0.004** (T5,T4>T1)	0.012* (T5>T1,T3)	0.311			

[a]Repeated Measures ANOVA

* Significant value (p <0.05), ** Significant value (p <0.01),***Significant value (p <0.001)

C= Controls; D=Depressed; M=Manic; E=Euthymic

T1-Baseline assessments, T2- Three months assessment, T3- Six month assessment, T4- Nine months assessment, T5- Twelve month assessment

Table 4: Cognitive performance across time periods in patient groups and controls: Tests for executive functions and working memory

Cognitive Domain (Measure)		BD-Depression median (min-max)	BD-Manic median (min-max)	BD_Euthymic median (min-max)	Controls median (min-max)	P value	Post-hoc (Wilcoxon signed rank-Bonferroni)
Executive Functions							
CTT-2(Time-in sec)	T1	217 (102-480)	231(95-325)	156 (32-402)	106 (60-242)	<0.001***	D,M,E>C; D,M>E
	T2	180 (100-468)	168 (0-307)	144.5 (69-375)	100.5 (60-242)	<0.001***	D,M,E>C
	T3	200 (119-480)	168 (0-338)	141.5 (80-290)	100.5 (60-242)	<0.001***	D,M,E>C D>E
	T4	185 (120-350)	168 (0-300)	140.5 (0-290)	101 (60-242)	<0.001***	D,M,E>C D>E
	T5	160 (113-300)	150 (0-300)	144 (56-319)	101 (60-242)	<0.001***	D,M,E>C
P value [d] (Post-hoc-Bon)[e]		<0.001*** (T3,T5>T1)	0.006** (T4,T5>T1)	0.040*	0.028*		
Stroop-interference[b]	T1	111 (0-465)	130 (55 -261)	100.5 (50-244)	60.5 (23-140)	<0.001***	D,M,E>C
	T2	99 (50-336)	110 (9-235)	86 (29-217)	60.5 (5-117)	<0.001***	D,M,E>C
	T3	83 (50-197)	83 (9-235)	67 (42-181)	60 (15-117)	.001**	D,M>C
	T4	100 (56-199)	.780	81.5 (26-197)	61 (31-117)	<0.001***	D,M>C
	T5	73 (55-155)	84 (29-235)	65 (29-158)	61 (31-117)	0.001**	D,M>C
P value [d] (Post-hoc-Bon)[e]		0.002** (T3,5>T1)	0.002** (T3,5>T1)	<0.001*** (T3,4,5>T1)	-		
Verbal N-back-1 (Hits)[b]	T1	8 (2-9)	7 (1-9)	8 (2-9)	9 (7-9)	<0.001***	C>D.M,E E>M
	T2	8 (5-9)	8 (1-9)	9 (1-9)	9 (8-9)	<0.001***	C>D.M,E
	T3	8 (4-9)	8 (1-9)	9 (3-9)	9 (8-9)	<0.001***	C>D.M,E E>M
	T4	7 (4-9)	8 (1-9)	9 (5-9)	9 (8-9)	<0.001***	C>D.M,E
	T5	9 (5-9)	8 (1-9)	9 (7-9)	9 (8-9)	<0.001***	C>D.M,E
P value [d] (Post-hoc-Bon)[e]		0.012*	0.045*	0.001** (T5>T1)	<0.001***		
Verbal N-back--2(Hits)[b]	T1	5 (0-7)	4(0- 8)	6 (1- 8)	7 (4- 9)	<0.001***	C>M,D,E
	T2	6 (1-7)	4(0- 8)	6 (2-9)	7 (5- 9)	<0.001***	C>M,D,E E>M
	T3	6 (2-9)	4 (0- 9)	6 (2-9)	7 (5- 9)	<0.001***	C>M,D,E E,D>M
	T4	5 (1-7)	6 (0-9)	6 (2- 8)	7 (5- 9)	<0.001***	C>M,D,E E>M
	T5	6 (2- 8)	5 (0-9)	7 (2- 9)	7 (5- 9)	<0.001***	C>D C,E>M
P value [d] (Post-hoc-Bon)[e]		0.024 *	0.137	0.052	0.118		

[a]Kruskal-Wallis Test; [b]Mann-Whitney Test; [c]Friedman Test; [d]Wilcoxon sign rank
** Significant value (p <0.01),***Significant value (p <0.001)
C= Controls; D=Depressed; M=Manic; E=Euthymic
T1-Baseline assessments, T2- Three months assessment, T3- Six month assessment, T4- Nine months assessment, T5- Twelve month assessment

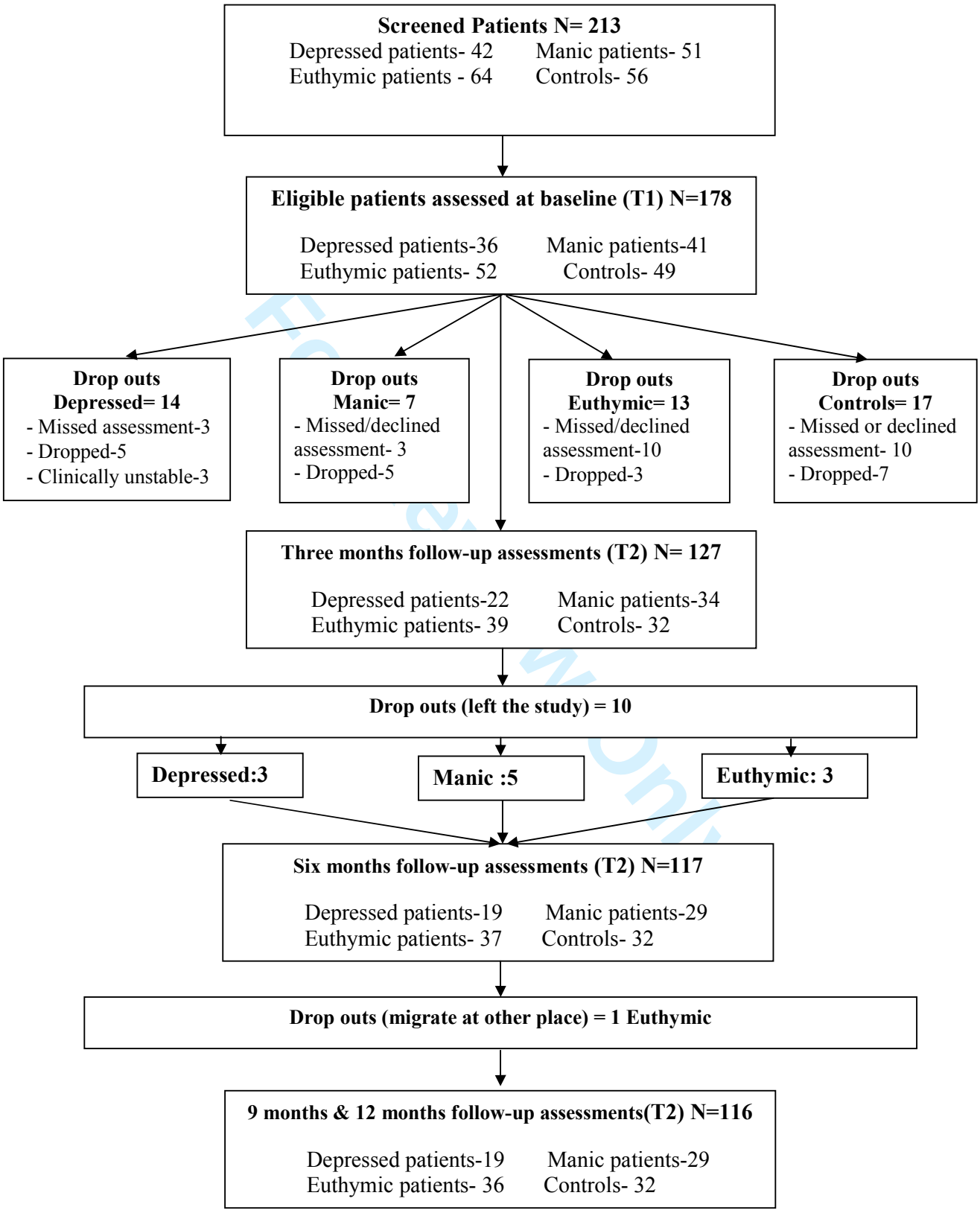

Figure 1: Flowchart to depict the sample at baseline and follow up assessments