Asian Journal of Psychiatry 44 (2019) 121–126

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Neurocognitive profile of patients with Bipolar Affective Disorder in the euthymic phase

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ARTICLE INFO

Keywords:
Bipolar disorder
Euthymia
Cognitive impairment
Executive functions
Memory

ABSTRACT

Bipolar disorder is a chronic psychiatric condition characterized by episodes of elevated/irritable and depressed moods resulting in the loss of more disability-adjusted life years (DALYs) than other major conditions. The neurocognitive impairments in these patients interfere with sustained goal-directed performance and achievement even during the euthymic phase of the illness.

Methodology: The study aimed to explore the neurocognitive profile of patients in their euthymic phase. We matched 30 patients diagnosed with Bipolar Affective Disorder (BD) in the age range of 20–40 years with 30 healthy controls (with no axis I or II diagnosis, assessed on MINI) matched on age, gender, and education. The neurocognitive profile was assessed using NIMHANS Neuropsychology Battery.

Results: Euthymic phase patients with bipolar disorder had statistically significant low scores on the speed of processing information as compared to healthy controls. Although impaired in BD group, no statistically significant difference was found between the two groups on executive functions and memory.

Conclusion: The findings of the study suggest that cognitive retraining aimed at ameliorating these deficits can be a used as an essential intervention in rehabilitation programs to successfully reintegrate patients with the bipolar affective disorder into the society. The research also indicates that despite the symptomatic recovery between the episodes, impairments in the speed of processing information continue to disrupt performance in patients with Bipolar Disorder.

1. Introduction

Bipolar Disorder (BD) is a chronic psychiatric condition characterized by alternating periods of elevated or irritable mood (mania/hypomania) and periods of depression. The hallmark of BD is emotional dysregulation, hence the quest for brain correlates of this disorder began with studies focusing on the limbic system (Papez, 1995). Research in past highlights the role of the limbic-cortical-striato-pallido-thalamic circuit (LCSPT) formed by connections between prefrontal cortex, amygdala, hippocampus, and subcortical structures in the etiology of mood disorders (Price and Drevets, 2010). These dysfunctional neural circuits in BD were assumed to provide an anatomical basis to cognitive impairments such as delayed information processing, attentional impairments, forgetfulness, emotional dysfunction, and executive deficits (mediated by PFC and its connections with the extended visceromotor network). The cognitive sequelae of this disorder- speed, attention, executive functions and memory impairments (Clark et al., 2002; Frangou et al., 2006; Martinez-Aran et al., 2004) are assumed to be reflected through symptoms such as impulsivity, poor judgement, and decision making observed during acute as well as remission periods (Bortolato et al., 2015; Bourne et al., 2013; Kolur et al., 2006; Robinson et al., 2006).

Neurocognitive basis of Bipolar Disorder (BD) explored during the symptomatic phase of illness has low reliability and impacts the generalizations of results (Mur et al., 2008). In an attempt to identify the vulnerability markers of BD, studies have explored if the cognitive

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https://doi.org/10.1016/j.ajp.2019.07.037
Received 18 August 2018; Received in revised form 20 July 2019; Accepted 23 July 2019

deficits observed in these patients are stable and continue from acute to remission phases of the illness thereby reflecting a trait feature of the illness (Clark and Goodwin, 2004; Daban et al., 2012; Mur et al., 2008). A systematic review of neuropsychological studies of BD between 1980 and 2000 found that cognitive abnormalities were seen in symptomatic BD patients and persisted in remission in measures of sustained attention and inhibitory control (Quraishi and Frangou, 2002). Cognitive slowing as well as deficits related to alertness, spontaneous flexibility, sustained, and divided attention have been consistently reported in euthymic patients with BD (Clark et al., 2002; Godard et al., 2011; Martinez-Aran et al., 2004; Mur et al., 2008; Zubieta et al., 2001).

Similar results were reported in another meta-analytic study describing attention, processing speed, memory, and executive dysfunction as trait markers of bipolar disorder (Torres et al., 2007). In particular, Mur et al (2008) conducted a 2 year follow up study to assess cognitive deficits in euthymic bipolar disorder patients. Results indicated that executive function and processing speed deficits continue across the remission phase of the illness and multi-level logistic regression analysis revealed processing speed impairments as an indicator of low work activity leading to poor work adaptation. However, contrary evidence exists indicating that executive dysfunction is a characteristic of the symptomatic phase of BD and is thus a state marker while speed and attention deficits are seen only in the euthymic phase of the illness and should be considered as the vulnerability marker of BD (Burdick et al., 2006; Maalouf et al., 2010). The authors suggested that selective attention deficits may be related to the phenomenology of BD and sustained attention (assessed using time-based tasks) deficits may represent a vulnerability marker for BD.

A meta-analytic review of longitudinal or prospective studies pertaining to neuroimaging or neuropsychological investigations in BD indicated that executive functioning deficits are present early and may persist, with some potential for improvement with treatment and during remission of BD (Lim et al., 2013). Another study (Daban et al., 2012) comparing 53 euthymic BD probands (BD-P), 50 unaffected first-degree relatives (UFDR) and 60 unrelated healthy controls (HC) revealed euthymic BD-P and the UFDR were significantly more impaired on DST performance even after controlling for demography and current mood symptoms (effect sizes 0.89 and 0.52). Authors concluded that processing speed may be a valid endophenotype, highly specific for differentiating both euthymic BD-P and UFDR, from HC.

However, important factors that can confound the results of these studies are the demographic factors such as age, education, chronicity of the illness, number of episodes, lack of standardized neuropsychological batteries and subthreshold affective symptoms (Bora et al., 2009). Therefore, we can argue that the holy grail of endophenotypes/trait marker of BD could only be uncovered by employing study designs that ensure patients are in remission phase, their neurocognitive profiles are assessed early in the illness course using standardized assessment tools and comparing them with demographically matched healthy controls. Hence, the aim of the present research is to examine the neurocognitive profile of patients with BD whose last mood episode was at least three months prior to their participation in the study (to ensure they can reliably perform assessments and are in remission) and comparing them with age, gender and education matched healthy controls. In the present study, patients with less than five episodes were taken to counter the chronicity effects of illness and treatment on cognition. Based on the existing literature, the authors hypothesize that processing speed and attention deficits would continue in the euthymic phase of bipolar disorder. It is crucial to study these factors as inter-episodic cognitive deficits may represent barriers for BD patients towards their reintegration in the normal repertoire of social and occupational functioning and consequently affect their quality of life (Brissos et al., 2008).

2. Methodology

A matched case-control design with cross-sectional assessment was used for the study.

2.1. Participants

The sample comprised of two groups- Bipolar group (BP) and matched healthy controls (HC) with n = 30 each. All participants were in the age range of 20–40 years and had minimum average intelligence (IQ > 90). The groups were matched on age (mean age of BP was 29.47 ± 5.52 years and HC was 29.13 ± 5.37 years); gender (23 males and 7 females in each) and years of education (16.20 ± 0.66 years in BP and 16.17 ± 0.79 years in HC group). The Bipolar group comprised of patients with a diagnosis of Bipolar Affective Disorder (as per ICD-10 criteria), seeking treatment from Outpatient Services of National Institute of Mental Health & Neurosciences (tertiary care centre in India). The inclusion criteria included meeting the criteria for bipolar affective disorder on MINI 6; a current euthymic mood state and a minimum of three months interval between their last mood episode and participation in the study. Individuals who had received ECT's or cognitive behavior therapy (CBT) as a part of their treatment and with more than 5 episodes of illness were excluded from the study. Various studies in the past have documented ECT's adversely affecting certain cognitive functions (Falconer et al., 2010; Getty and Faziola, 2017) and including participants who have received ECT in the study could have confounded the findings. Cognitive Behaviour Therapy is also aimed at restructuring cognitive processes leading to reduced impulsivity, increased reasoning, response inhibition, planning and decision making thereby positively impacting cognitive functions (Brooks and Stein, 2015; Frewen et al., 2008; Porto et al., 2009) and hence was an exclusion criterion. Participation in the study did not involve any change in their on-going treatment, and most patients received a combination of antidepressant and antipsychotic medication. While medications are also known to affect cognitive functions, it could not be made an exclusion criterion as the majority of patients receive medications after their first episode and assessing cognitive profile in the acute phase of illness was not the objective of the current study. Control group comprised of normal, healthy adults from the community matched with the BP group on age, gender, and education. Individuals with any medical, psychiatric (except BD for the Bipolar group) or neurological disorders were excluded from the study. Written informed consent and socio-demographic details were obtained from all the participants (enquiring details like age, gender, education, course and duration of illness) in a socio-demographic datasheet and supplemented with information from the clinical case file and the study was approved by the Institute Ethics Committee.

2.2. Material & procedure

Edinburgh Handedness Inventory (Oldfield, 1971) was used to determine the handedness. It has ten simple items of day to day activities and assesses handedness using the laterality quotient.

2.2.1. Intelligence

Raven's Standard Progressive Matrices (RPM) (Raven, 1938) was used to assess intelligence. It consists of 60 problems presented in the form of 5 sets containing12 each. These problems involve completing a pattern or figure with a part missing by choosing the correct missing piece from among six alternatives.

2.2.2. BD diagnosis

Mini-International Neuropsychiatric Interview (M.I.N.I. 6.0) (Sheehan et al., 1998) a short, structured diagnostic interview used to confirm the diagnosis of BD in the BP group and exclude any co-morbidities.

2.2.3. Disease severity

Young Mania Rating Scale (YMRS) (Young et al., 1978) was used to assess the presence and severity of manic symptoms.

2.2.4. Depressive symptoms

Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was used to assess the presence of and severity of depressive symptoms.

2.2.5. Comprehensive neuropsychological profile

NIMHANS Neuropsychological Battery (Rao et al., 2004) was used to assess a comprehensive neuropsychological profile of participants. The battery comprises of globally recognized neuropsychological tests which have been standardized on a normative sample of Indian adults between the age range of 16–65 years. The normative data has been classified according to age, gender, and education and is in the form of percentiles which are an objective index of brain dysfunction. The battery has been validated on patients with focal lesions, head injury, intractable epilepsy, and movement disorders. NIMHANS Neuropsychology battery has been extensively used to assess cognitive deficits in various clinical conditions (Bennett et al., 2018; Rajeswaran and Nalini, 2013; Reddy et al., 2013, 2017; Solanki et al., 2017). Percentile scores obtained on these tests were used for cross-sectional comparison of the two groups.

The tests were administered in a balanced manner and adequate rest breaks were provided to the participants during the administration to reduce fatigue and monotony. The battery took approximately three hours of administration for each participant.

Three major neuropsychological domains were assessed namely:

The domain of Speed and Attention- a) Speed of Information Processing was assessed using the Digit Symbol Substitution Test (Wechsler, 1981). The test consists of a sheet in which numbers 1–9 are randomly arranged in 4 rows of 25 squares each. The subject substitutes each number with a symbol using a number-symbol key given on the top of the page. b) Attention was assessed using the Colour Trails Test (CT) (D' Elia et al., 1996). It has two parts. Part 1 (CT1) requires sustained attention, perceptual tracking, and simple sequencing while Part 2 (CT2) requires mental flexibility in addition to the above. The time taken to complete the task in each part forms the score.

Executive Functions Domain- a) Category Fluency was assessed using Animal Names Test (ANT) (Lezak, 1995). It requires the subject to generate names of animals excluding names of fishes, birds, and snakes for one minute. The number of animals reported forms the score. b) Visual Fluency was assessed using the Design Fluency Test (Jones-Gotman and Milner, 1977). It measures the ability to produce novel designs. The designs should not represent actual objects or nameable abstract forms and should not be reproduced from memory. There are two conditions to this test. In the Free condition, the subject is given five minutes to draw new designs. In the Fixed condition, the subject draws in four minutes, novel designs with the restriction that only four straight or curved lines may be used per design. The score in each condition is the number of novel designs produced. c) Verbal Working Memory was assessed using **N**-back tests (Smith and Jonides, 1999). It consists of a list of phonemes common to various Indian languages and is presented auditory at the rate of one per second. One back requires the participant to say yes for a consecutively similar phoneme being read out at the rate of one per second. Two back requires the participants to say yes for every alternatively similar phoneme. The number of correct responses in each part of the test comprises the score. d) Visuospatial Working Memory was assessed using the Spatial Span Test (Milner, 1971). The test comprises of a board with 10 cubes arranged haphazardly. The examiner taps the blocks according to a sequence given in the test form, which the subject is required to repeat. In the Forward condition, the subject is asked to tap the same blocks in the same order as an examiner and the backward condition subject is asked to tap the blocks in reverse order. The total score is calculated by combining the forward and backward score. e) Planning was assessed using the Tower of London Test (TOL) (Shallice, 1982). The subject is presented with a goal state of the arrangement of three balls on one of the boards. The arrangement of the ball on the other board is the initial state. The subject must arrive at the goal state in the board placed on the subject side following the rules provided by the examiner. Time taken and number of moves used to reach the target forms the score. f) Set Shifting Ability was assessed using the Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993) was used to assess. The subject's capacity to form a mental set is measured by how quickly he/she attains the concept and retains it without any error for 10 consecutive trials. The test is terminated after the subject attains all the 6 concepts or after all the 128 cards have been used. The number of cards used to complete all 6 categories form the score for concept formation. g) Response Inhibition was assessed using the Stroop Test (Rao et al., 2004). The color names **"Blue,"** **"Green,"** **"Red"** and **"Yellow"** are printed in capital letters in same/other colors on a paper. The subject is asked to read the stimuli column-wise as fast as possible. Next, the subject is asked to name the color in which the word is printed. Time taken to complete the second task is subtracted from the first reading, thus giving the interference time which in turn forms the score.

Memory Functions- a) Verbal Learning and Memory was assessed using the Auditory Verbal Learning Test (AVLT) (Schmidt, 1996). It consists of a list of 15 words presented five times with an immediate recall after each of the five trials. The delayed recall is taken after a delay of 20 min filled with other nonverbal tests. The number of words recalled from the list form the score. b) Visual Learning & Memory was assessed using the Complex Figure Test (CFT) (Meyers and Meyers, 1995). At the first step, subjects are given the CFT stimulus card, and then the subject is asked to copy the figure without using a ruler to draw. The immediate recall trial is administered 3 min after the copy trial, and 30 min after the copy trial, the subject is asked to draw the figure from memory. The complex figure design comprises of 18 figural elements and each element is given 1 score for accuracy and 1 score for the correct location, thereby giving a maximum total score of 36. The number of elements correctly placed and accurately drawn forms the total score for each participant.

2.3. Data analysis

Neuropsychological tests were scored using specific test guidelines. We used SPSS 20.0 version to analyze the data. The descriptive analysis for continuous variables and frequency analysis of qualitative variables is presented in Table 1. Shapiro-Wilk's test (Shapiro and Wilk, 1965) was used to test the normality of distribution. The categorical data was analyzed using the chi-square test. The non-parametric tests were used for comparison of groups as the data did not meet the assumptions of normality. Since each subject in a group was matched with the other in the first group, scores were analyzed using Wilcoxon Sign Rank test for matched paired data. A value of $p < 0.05$ was considered statistically significant.

3. Results

The demographic details of the sample along with the clinical profile of the BP group are presented in Table 1. Participants in both groups were right-handed. There is no significant difference between the two groups on age, years of education and cross-sectional scores on YMRS indicating the absence of any manic symptoms. However, results reveal a significant difference between the two groups on cross-sectional depression ratings as indicated by HDRS with BP group attaining higher scores on depression but are below the criteria for depression on HDRS.

A statistically significant difference was found between the two groups on the speed of processing information indicating poor mental speed in euthymic patients with BD. Although, no statistically significant difference was found between the two groups on executive functions and memory (Table 2, Fig. 1).

Table 1
Comparison of age and education between Bipolar Disorder group (BP) and Healthy Controls (HC).

Variables	Bipolar group (n = 30) Mean ± S.D.	Healthy Control (n = 30) Mean ± S.D.	P Value
Age (Years)	29.47 ± 5.52	29.13 ± 5.37	0.08
Education (Years)	16.20 ± 0.66	16.17 ± 0.79	0.80
YMRS	0.23 ± 0.971	0.00	0.18
HDRS	2.03 ± 2.723	0.00	**0.00**
Duration of Illness (years)	7 ± 4.97	–	–
No of Episodes	3.43 ± 1.25	–	–

Variables		Bipolar group (n = 30)		Healthy Control (n = 30)		P Value
		n	%	n	%	
Marital Status	Single	14	46.7	18	60.0	0.40
	Married	15	50.0	12	40.0	
	Divorced	1	3.3	0	0.0	
Employment	Employed	26	86.7	30	100	0.38
	Unemployed	4	13.3	0	0.0	
Family History of Psychiatric Illness	Positive	12	40.0	4	13.3	**0.02**
	Negative	18	60.0	26	86.7	

Table 2
Comparison of Neuropsychological functions between Bipolar and Healthy Control group (Values are percentile scores obtained by each group on specific test).

Variables	Bipolar Group (n = 30) Mean ± S.D.	Healthy Control (n = 30) Mean ± S.D.	P-value
Mental Speed (DSST)	44.47 ± 31.15	72.13 ± 31.97	**0.002****
Attention (CT)	36.40 ± 32.75	41.95 ± 24.00	0.41
Category Fluency (ANT)	38.42 ± 28.10	40.75 ± 32.09	0.6
Design Fluency Free (DFFR)	51.75 ± 31.21	42.33 ± 24.11	0.17
Design Fluency Fixed (DFFX)	60.33 ± 32.40	50.25 ± 23.98	0.2
Verbal Working Memory (N Back)	46.83 ± 26.53	42.58 ± 25.08	0.37
Visuospatial Working Memory (SPSS)	41.08 ± 38.94	45.83 ± 37.40	0.34
Planning (TOL)	71.10 ± 19.48	65.87 ± 23.67	0.41
Set Shifting (WCST)	53.43 ± 32.42	55.87 ± 29.04	0.85
Response Inhibition (STROOP)	45.25 ± 36.73	58.58 ± 29.78	0.08
Verbal Memory (AVLT)	51.08 ± 27.99	40.17 ± 25.27	0.07
Visual Memory (CFT)	36.67 ± 31.67	37.25 ± 27.93	0.93

4. Discussion

The current study investigated the cognitive profile of patients with bipolar disorder in their euthymic phase by comparing them with healthy controls. The cognitive profile of illness provides valuable insights into its neuroanatomical etiology/mechanism and guides intervention programs aiming at successful reintegration of patients into society. Bipolar disorder has been characteristically understood as an episodic illness distinguished by periods of absolute/near-complete recovery. However, studies in the recent past have attempted to unravel disease-specific cognitive deficits persisting even in the euthymic phase of the illness. These specific cognitive variables could be considered as vulnerability/trait-specific markers of the disorder and enrich our understanding and management of these patients. However, demographic variables such as age, gender, education; and illness-related factors (duration of the illness, number of episodes and long-term use of medications) can confound the cognitive profiles obtained from patients in their euthymic phase. Hence, the current study is designed to include groups matched one to one on age, gender and education, while controlling the illness-specific factors. Illness-related factors in the BP group were controlled by including patients who had a euthymic mood state for at least four weeks prior to their participation in the study and a minimum of three months interval between their last mood episode and participation in the study. The number of episodes experienced in their clinical history were restricted to an upper limit of five.

On demographic analysis, a significant difference was found between the two groups on the presence of a family history of psychiatric illness. 40% of the BP group reported a positive family history of psychiatric illness as compared to 13% in the healthy control (HC) group. A high prevalence rate reported in the BP group reiterates the existing notion of heritability of this disorder (Barnett and Smoller, 2009; Smoller and Finn, 2003). Also, of interest are the cross-sectional scores on mania and depression rating scales at the time of participation in the study. Though the BP group comprised of euthymic patients and no statistically significant difference was found between the two groups on YMRS. The depression ratings in HDRS were different with BP group reporting residual symptoms of depression (did not meet the criteria for syndromal depression). This is in congruence with previous studies that have reported patients with bipolar disorder (euthymic) and major depressive disorder individuals report increased use of rumination, catastrophizing, and self-blame alongside the decreased use of positive reappraisal, and putting into perspective as compared to healthy controls (Wolkenstein et al., 2014).

A comparison of two groups on cognitive functioning revealed significant deficits in the speed of processing information in the BP group, indicating the persistence of mental speed deficits even in remission (Maalouf et al., 2010). The results of the present study partially accept our hypothesis based on the previous studies that describe only attention and speed deficits in euthymic BD and executive and memory dysfunction as state markers of BD, present only during the symptomatic phase (Arts et al., 2011; Burdick et al., 2006; Fakhry et al., 2013; Harmer et al., 2002; Maalouf et al., 2010; Meyer et al., 2004; Robinson et al., 2006). Our findings of statistically significant decreased processing efficiency with adequate sustained attention in euthymic patients with BD could be explained using the processing efficiency theory (Eysenck and Calvo, 1992) indicating speed-accuracy trade-off by BP group to perform as effectively (accurately) as healthy controls on focused attention tasks. It supports previous studies' (Fleck et al., 2005) contention that cognitive reorganization in the euthymic phase of illness may allow disrupted automatic processes to be performed through effortful control at the expense of processing efficiency.

Several large-scale studies comparing unaffected first-degree relatives of patients with BD and healthy controls have reported processing speed deficits as underlying vulnerability factors to BD with large effect size (Antila et al., 2007; Daban et al., 2012; Frantom et al., 2008; Glahn et al., 2010). Our results also support the inferences made in

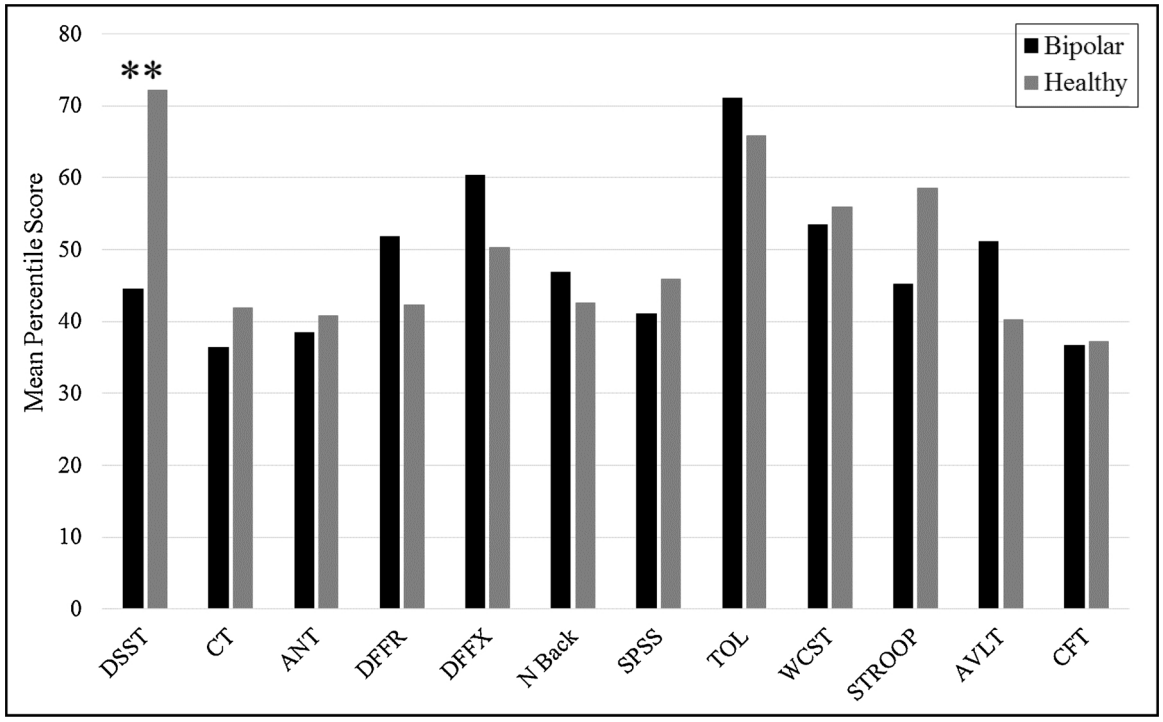

Fig. 1. Comparison of Neuropsychological functions between Bipolar and Healthy Control group.

previous studies that processing speed assessed using Digit Symbol Substitution task in the euthymic phase of the illness may be a valid cognitive endophenotype of BD (Daban et al., 2012; Thompson et al., 2005).

Kraepelin had described the euthymic phase of BD as "normality" in essence and had used it as a fulcrum to discriminate episodic illness like BD from a chronic disorder like schizophrenia (Malhi et al., 2004). However, findings of the current study indicating processing speed deficits in euthymic patients (especially with not more than 5 episodes of illness) provide insights into chronicity of this illness and would have implications in formulating management and rehabilitation plans for these patients.

The study has a methodological strength in one to one matching across both groups, thereby controlling for the influence of age, gender, and education. There were limitations in terms of small sample size (30 in each group) and gender differences in cognition could not be studied. Also, the effects of drugs on cognition could not be studied. Studies in past have also reported the challenges associated with maintaining this limitation as it is difficult to find drug-naive patients with a similar number of episodes and it would be unethical to withhold medications for research purposes in patients using them for clinical purposes. Also, strong evidence suggests that the amount of variance in DST speed explained by psychotropics is negligible compared to other factors and that deficits in the DST observed in euthymic BD patients remain stable even when medication use is considered (Bearden et al., 2001; Daban et al., 2012; Glahn et al., 2010; Lopez-Jaramillo et al., 2010; Thompson et al., 2005). In future cognitive assessments could also be supported by neuroimaging evidence and studies could explore the effects of chronicity of illness and psychosocial factors such as interpersonal attachments, employment stability, and social support.

Source of funding

None.

Declaration of Competing Interest

None.

Acknowledgement

None.

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