Review article

Cognitive dysfunction as a trait marker for Bipolar disorder: A critical review

Raman Deep Pattanayak, Rajesh Sagar, Manju Mehta

Abstract

Cognitive impairments have been found in euthymic period of BD and have been projected as a core feature of BD. We review the available research to evaluate if cognitive dysfunction could possibly serve as a trait marker for BD. Evidence suggests that certain cognitive impairments are present very early in the course of illness, persist in euthymia, present in first degree relatives and cannot be fully explained by medication effects or subsyndromal symptomatology. Several questions remain unanswered and more research is required in order to delineate the origin of cognitive dysfunction.

Introduction

Recent research has challenged the traditionally held view of bipolar disorder (BD) as a purely episodic illness with complete clinical and functional recovery between the episodes. A large proportion of BD patients fail to regain the functioning even after resolution of major affective symptoms.[1,2] The cognitive impairments have been found to persist in euthymic period, which can influence the psychosocial outcomes and explain the gap in clinical and functional recovery in a subgroup of patients.[3-5] Initial studies on cognition in BD were fueled by the controversy whether BD and schizophrenia are separate disorders or on a continuum.[6,7] As the initial evidence reported cognitive impairments in BD, more interest was generated due to their potential diagnostic as well as treatment implications. Over the past few years, there have been attempts to search intermediate endophenotypes or markers for various psychiatric disorders including BD.[8] The cognitive dysfunction has been projected as a trait marker, a core feature and a potential endophenotype for the BD.[9,10]

We review the literature to evaluate if cognitive dysfunction could possibly serve as a trait marker for BD.

Cognitive Impairments in Euthymic Patients

In the clinical setting, many BD patients do complain of persistent difficulties in concentration, memory, inability to perform optimally in challenging tasks or even, in day to day functioning. While a variety of factors may be responsible for persistent functional impairments, at least a subgroup of patients are likely to experience poor psychosocial outcomes as a result of cognitive dysfunction.[4,5] Recent studies indicate that as many as 60% of BD patients are cognitively impaired at a level deemed to be

clinically relevant during periods of affective remission.[11]

Neuropsychological assessment of broad domains of executive functions, memory and attention/psychomotor speed has documented cognitive deficits in euthymic BD-I patients in a number of studies over the past decade. The cognitive deficits with robust evidence base are psychomotor speed, sustained attention, verbal learning and memory, response inhibition and set-shifting. The severity of the cognitive deficits in euthymic patients is medium to large in magnitude, based on reported effect sizes across several recent meta-analyses,[12-15] summarized in Table 1. Euthymic BD patients do not have a broad dysexecutive syndrome, rather a more selective impairment. The cognitive deficits in euthymic BD appear to be consistent cross-culturally as studies from several centres across the world generated similar effect sizes.

Qualitatively similar deficits have been found in BD-II patients as well, though majority of evidence suggests that these deficits are lesser in severity compared to BD-I.[16,17] For example, in the study by Torrent et al,[16] verbal memory and stroop test performances of BD-II patients were better than BD-I patients and worse than the control group There was, however, no significant difference in attention and psychomotor speed dysfunctions. There is some contradictory evidence to suggest that perhaps some of the deficits may be severe in BD-II, conditional to repetitive depression, as indicated in the study by Summers et al [18] where memory and executive functions were worse in BD-II patients compared to BD-I patients.

Table 1: Summary of meta-analytic studies for cognitive deficits in euthymic BD

Meta-analysis	Number of studies	Number of subjects	Findings
Robinson et al, 2006[12]	26	689 patients; 721 controls	*Large ES*: Executive function (category fluency, mental manipulation), verbal learning *Medium ES*: Immediate and delayed verbal memory, abstraction and set-shifting, sustained attention, response inhibition, psychomotor speed *Small ES*: Verbal fluency by letter, immediate memory, and sustained attention
Torres et al, 2007[13]	39	948 patients; 1128 controls	*Medium ES*: Attention/processing speed, immediate and delayed recall, executive functioning
Arts et al, 2008[14]	28	679 patients; 780 controls	*Large ES*: Executive functions (working memory, executive control, fluency) and verbal memory *Medium ES*: Executive function (concept shifting, executive control), mental speed, visual memory, and sustained attention *Small ES*: Visuoperception
Bora et al, 2009[15]	45	1423 patients; 1524 controls	*Large ES*: Set shifting, verbal learning, sustained attention *Medium ES*: Response inhibition, psychomotor speed, immediate and delayed recall *Small ES:* Visual memory, verbal recognition

ES: Effect size; Large ($d > 0.8$), Medium ($0.5 > d < 0.8$); Small ($d < 0.5$); Controls: Healthy individuals

Cognitive Dysfunction in BD: Longitudinal Perspective

The onset of cognitive deficits in BD has not been well-studied. Studies of large national samples[19,20] of people who joined army and later on developed a psychiatric disorder have shown mixed results and could not clarify if the cognitive deficits predate the clinical onset of disorder. For example, a study from Israel [19] showed that individuals who later on developed non-psychotic BD did not have cognitive deficits at the time of army recruitment, in contrast to individuals who developed schizophrenia. In another study,[20] the risk for developing a disorder was calculated on basis of available information along with intellectual assessment of apparently healthy army recruits and BD figured highest in relative risk on basis of performance in visuo-spatial reasoning.

Evidence suggests that cognitive impairments are present at first episode[21] and persist over time.[22,23] The cognitive deficits, particularly delayed verbal memory, may worsen with repeated acute episodes and number of hospitalizations, and with somewhat mixed evidence, may worsen with increasing duration of illness or psychotic episodes.[24] There have been a few longitudinal studies to investigate whether the cognitive deficits progress, persist or remit over time in individuals with BD. In a recent two-year naturalistic study[25], with repeated two-monthly assessments, the cognitive functions were found to vary significantly over time, largely independent of clinical factors, with the exception of sustained attention and motor speed which were invariant over time. In another study,[26] patients with BD-I were assessed over a period of 30 months in various phases of illness. Euthymic state was associated with impaired recall, though some other deficit were found to be better compared to the mood states.

The presence of cognitive impairments in acute manic as well as depressive states has been well-documented.[27,28] Cognitive dysfunction in BD tends to be most severe and least differentiated during acute mood disturbance, when significant deficits in impulsivity, attention, and executive functioning are evident.[29] In some studies, executive dysfunction has been found to be highest in manic patients compared to euthymic and depressed patients.[9] When compared with their performance in the manic state, euthymic patients had better visuospatial recognition memory, improved accuracy on tasks of executive function and better vigilance.[30,31] Available studies point to impairment in attention, executive dysfunction and decision-making in depression.[9] Depressed phase has also been associated with memory and psychomotor impairments compared to euthymic phase.[26] It appears that each of the mood states (mania, hypomania, depression, and euthymia) is associated with cognitive impairments, particularly in the domains of memory and executive function,[9,29] though the euthymic state is associated with less impairments than the other states. A few studies [32,33] have tried to establish if the length of time in clinical remission prior to neuropsychological testing had a relation to the test performance, but found no significant association between duration of euthymia and performance on various tests.

The stable, trait-like presentation of at least some cognitive impairments during euthymia raises a possibility that these may be related to aberrant neurodevelopment or to a genetic vulnerability for bipolar illness. However, it is to be pointed out that further studies are required to document the long-term course of cognitive impairments across time and mood states.

Cognitive Impairments in Unaffected Relatives

A range of neuropsychological impairments have been found in studies in first degree relatives (parents, sibling, children) of patients with BD. There is evidence that executive dysfunction and working memory dysfunction [32,33] are present in the relatives of BD patients, while a few other studies[34] indicate the presence of only ventromedial frontal cortex dysfunction. Mixed evidence had emerged for verbal memory and sustained attention deficits.[9,29] In the two meta-analytic studies[14,15] of first degree relatives available so far and summarized in Table 2, the effect sizes were relatively small, but nonetheless significant differences were present compared to healthy individuals. In particular, the response inhibition measured by stroop task had a medium effect size, which also emerged strongly in the studies on BD patients and could be one of the possible trait markers.

Interestingly, a few twin studies[35-37] are available for BD, in which one of twins had BD and the twin-pair were compared with healthy control monozygotic twins. Impairments in working memory and verbal memory were found in BD twins[35] and verbal dysfunction was found only in the female twins.[36] The healthy twin of BD patient had dysfunctions in language, memory, executive functions, sustained attention and working memory.[37] Relative studies have set forth evidence that cognitive dysfunction can be an evidence of genetic risk and serve as a trait marker for the disorder.

Table 1: Summary of meta-analytic studies for cognitive deficits in first degree relatives

Meta-analysis	Number of studies	Number of subjects	Findings
Arts et al, 2008[14]	14	350 relatives 592 controls	*Small ES*: Executive functions *Medium ES:* Response inhibition
Bora et al, 2009[15]	17	443 relatives; 797 controls	*Small ES*: Executive functions, verbal memory, sustained attention

Effect size (ES)- small (d < 0.5), medium (0.5 > *d* < 0.8); Controls: Healthy individuals

Contribution of Indian Research

Few Indian studies are available which have investigated various aspects of cognitive dysfunction in BD patients[38-45] and the unaffected relatives[46,47] Broadly, similar profile of cognitive deficits emerged as in international literature. Significant deficits were found in executive functions[38,39] verbal memory[38,40,41] attention,[38,40] information processing speed and cognitive flexibility[40] in the euthymic BD patients compared to healthy controls. In contrast to many international studies, first episode patients were found to be more impaired in several cognitive domains compared to multi-episode as well as healthy controls.[42] This finding needs to be replicated in future Indian work as well and if established, can provide new insights. Cognitive deficits in BD were somewhat similar, though less severe than schizophrenia.[43,44] In a study comparing the medicated and drug-free euthymic BD patients,[45] only the delayed verbal recall and perseverations during the five-point test were found to differ and that too became insignificant when residual mood symptoms were controlled statistically, indicating that possibly medications did not have a significant influence on neurocognitive performance. This is one of the few studies on unmedicated BD patients. In a study of BD relatives,[46] they performed significantly poorly on tests for executive function and vigilance

compared to healthy controls, while in another study, unaffected siblings were found to have deficits in verbal learning and memory as well as executive functions.[47]

Origin of Cognitive Dysfunction: Illness or inherent?

The evidence for specific neurocognitive links to various brain abnormalities that explain the extent and nature of the impairment is still preliminary, inconsistent and unclear. However, two broad hypothesis are proposed and being evaluated with gradual accumulation of evidence.

Evidence indicates that chronic, multiple-episode patients exhibit more severe cognitive impairments than younger patients or patients with a more remitting course of illness. This may reflect longstanding neurophysiologic insults brought about by prior affective or psychotic episodes and/or long-term treatment for those episodes. The neurodegenerative hypothesis suggests that the chronic stress of mood instability carries neurotoxic effects, leading to neurological damage, neuronal loss and resultant cognitive decline over time.[10, 48] It stems from evidence generated by several studies which have indicated a positive correlation between overall illness severity (number of episodes, hospitalizations, duration of illness etc) and patient's level of cognitive dysfunction.[12,13,24] This, coupled with evidence of general reduction in brain volume, longitudinal connections between cognitive and neurological decline, and excessive physiological morbidity and mortality due to a host of comorbid conditions,[48] supports the neurodegenerative account.

In parallel, there has been an increasing stress on a neurodevelopmental hypothesis, especially as the available evidence does not fully support neurodegeneration in BD. From a neurodevelopmental perspective, brain and cognitive dysfunction may exist even prior to onset of first episode in patients with BD. Studies suggest that cognitive dysfunction is present from a very early stage of disorder,[49] though as discussed earlier the onset per se is not well-researched. The cognitive impairments do not show a universal progression with illness, for example in a study of children with BD with a 11.7 years follow-up, the developmental progress in executive functioning and verbal memory was significantly less in patients with BD than in the healthy controls.[50] The compelling evidence of cognitive dysfunction in unaffected and apparently healthy relatives of BD, discussed in detail earlier, strongly supports the hypothesis. The neuroimaging abnormalities reported in several regions of the brain early in the course of BD,[51,52] appear to be consistent the neurodevelopmental hypothesis, for example Zimmermann et al[53] reported a relationship between decrease in the volume of frontal cingulate regions and executive dysfunction.

In many ways, the neurocognitive research is linked to and has the potential to contribute towards the larger and ongoing debate for etiology of BD and other major psychiatric disorders.

Methodological issues and concerns

Cognitive impairments associated with euthymic BD patients may be confounded by multiple clinical variables, which may be manifestations of subclinical affective symptoms or broader epiphenomena of illness history or could be influenced by treatment or medication effects. Most of earlier studies did not define the presence of euthymia using standard tests and at times, ethical considerations have made it difficult to conduct research on unmedicated patients. Consequently, it is important to bear in mind the

methodological limitations while interpreting the research. More recent studies have, however, tried to limit the influence of these clinical and/ or treatment variables on neuropsycholgical performance as far as possible.

Presence of subclinical affective states: The type and severity of cognitive deficits are relatively less in recent studies where euthymia is clearly established compared to previous studies with questionable remission.[9] Euthymic BD patients often present with minor affective symptoms, which may adversely affect performance on cognitive measures.[9,10] A few studies have tried to account for very mild dysphoric or depressive symptoms in otherwise euthymic patients and found that even after statistically controlling for these subsyndromal symptoms, there was still an impairment in visuospatial recognition memory,[30] sustained attention[32] and executive function.[33]It appears that euthymia is associated with at least some cognitive deficits despite carefully ruling out mood symptoms.

Effect of medication on cognitive functions: For clinical and ethical reasons, it is difficult to obtain a sample of unmedicated bipolar patients especially since the cognitive studies are mostly based in a hospital setting. The psychotropic medications can have cognitive adverse effects, which may reflect in the neuropsycholgical performance. A meta-analysis[15] of lithium effects on cognition indicated small but statistically significant deleterious effects on immediate verbal learning and memory. Studies do indicate a possible relationship of treatment to cognitive impairments in BD. However, these studies do not completely explain the cognitive dysfunction in remission. There are a few interpretation difficulties for studies, which investigate the relationship between cognitive dysfunction in BD and medication use because the differences in medicated patients may be arising from other diverse characteristics of the groups rather than the effect of the drugs. Further, some studies did not find any difference for cognitive functions between medicated and unmedicated patients.[54]

Possible influence of illness variables on cognition: Several illness variables e.g. age of onset, number of total , manic or depressive episodes, illness duration, history of psychotic symptoms, number of hospitalizations, comorbid psychiatric/ substance use/ medical disorders etc have been found to be associated with higher cognitive deficits in euthymia, though evidence remains mixed for some of the variables.[9,29] Until recently, these variables have not been described clearly in many of available studies leading to heterogeneity of findings. However, it may not necessarily mean that the cognitive dysfunction is the result of more severe illness. It may also mean that the more severe, psychotic BD could represent a distinct, more homogenous subtype of the disorder and may be associated with specific cognitive deficits as vulnerability markers. Further research is needed to delineate the precise relationship.

A Potential Endophenotype?

Endophenotypes are measurable markers along the pathway between disease and distal genotype. Using endophenotypic markers may be advantageous as they are generally less complex and less heterogeneous than their associated clinically defined phenotype and thus, may be more readily linked to a specific genetic locus. Endophenotypes may have additional uses in psychiatry, including uses in diagnosis, classification, and the development of animal models.[8] In order for a cognitive measure, or any marker, to be considered an endophenotype, it must be (1) highly heritable, (2) associated with the illness, (3) independent

of clinical state, and (4) must co-segregate with the illness within a family, with non-affected family members showing impairment relative to general population.[10] The cognitive functions are highly heritable. Cognitive domains such as attention, executive functioning, processing speed, working and declarative memory are strongly influenced by genetics,[55] which account for nearly 50-80% differences in the sample. The cognitive deficits have been associated with illness, particularly in the euthymic phase as well as first degree unaffected relatives. The cognitive impairments, particularly executive functions and verbal memory, appear to fulfill all the criteria for a consideration as possible endophenotype of BD.

Future Directions

Future research should carefully try to differentiate cognitive deficits associated with disease genotype from impairments related to other confounding factors. Longitudinal studies for stability of euthymic cognitive deficits over lifetime would be immensely useful. The onset of cognitive dysfunction in BD merits a special attention, with more studies focusing on neuropsychological performance before the onset of illness as well as in very early stages. It is particularly important to determine which aspects of cognitive impairments meet the trait criteria. Data from family studies have very recently begun to address the question of the possible familial aggregation of cognitive impairment in relatives of patients with BD. Relatively less studies have focused on family members of BD and future research should focus more on unaffected relatives, possibly with larger samples, to provide evidence for cognitive trait markers. It also needs to be seen if BD share some of the probable endophenotypes with other disorders like schizophrenia. The research must proceed with lessons from research on other medical disorders with similar complex inheritance patterns. It can borrow some of methodological concepts from cognitive research in schizophrenia which was initiated at least a decade before BD. There is a need for greater integration and linkage of the findings from cognitive research in BD with advances in neuroimaging, molecular biology and genetics.

Conclusion

The cognitive dysfunction in BD appear to be related both to a trait predisposition and illness progression. However, certain cognitive deficits are present very early in the course of illness, persist in euthymic patients and are present in first degree relatives of BD patients. The confounders such as medication effects or subsyndromal symptomatology cannot fully explain the presence of cognitive dysfunction in euthymic patients. A least, some of the cognitive impairments do fulfill all the criteria for a probable endophenotype of BD. However, several questions remain unanswered and more research is required in order to delineate the origin of cognitive dysfunction.

References

1. Goldberg JF, Harrow M, Grossman LS. Course and outcome in bipolar affective disorder: a longitudinal follow-up study. Am J Psychiatry 1995; 152: 379-84.
2. DelBello MP, Hanseman D, Adler CM, Fleck DE, Strakowski SM. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. Am J Psychiatry 2007; 164: 582-90.
3. Thompson JM, Gallagher P, Hughes JH, Watson S, Gray JM, Ferrier IN, et al. Neurocognitive impairment in euthymic patients with bipolar affective disorder. Br

J Psychiatry 2005; 186: 32-40.
4. Martinez-Aran A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, et al. Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 2004; 6: 224–32.
5. Atre-Vaidya N, Taylor MA, Seidenberg M, Reed R, Perrine A, Glick-Oberwise F. Cognitive deficits, psychopathology, and psychosocial functioning in bipolar mood disorder. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 120-26.
6. Hill SK, Harris MS, Herbener ES, Pavuluri M, Sweeney JA. Neurocognitive allied phenotypes for schizophrenia and bipolar disorder. Schizophr Bull 2008; 34: 743-59.
7. Harvey PD, Wingo AP, Burdick KE, Baldessarini RJ. Cognition and disability in bipolar disorder: lessons from schizophrenia research. Bipolar Disord 2010; 12: 364-75.
8. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160: 636-45.
9. Bora E, Vahip S, Akdeniz F. The Role and Importance of Cognitive symptoms in Bipolar Disorder. Turkish J Psychiatry 2008; 19: 81-93.
10. Glahn DC, Bearden CE, Niendam TA, Escamilla MA. The feasibility of neuropsychological endophenotypes in the search for genes associated with bipolar affective disorder. Bipolar Disord 2004; 6: 171–82.
11. Martino DJ, Strejilevich SA, Scapola M et al. Heterogeneity in cognitive functioning among patients with bipolar disorder. J Affect Disord 2008; 109: 149-56.
12. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. A metaanalysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 2006; 93: 105-15.
13. Torres IJ, Boudreau VG, Yatham LN. Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand 2007; 116 (Suppl 434): S17-26.
14. Arts B, Jabben N, Krabbendam L, van Os J. Metaanalyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 2008; 38: 771-85.
15. Bora E, Yucel M, Pantelis C. Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 2009; 113: 1-20.
16. Torrent C, Martinez-Ara´n A, Daban C, Sánchez-Moreno J, Comes M, Goikolea JM, et al. Cognitive impairment in bipolar II disorder. Br J Psychiatry 2006; 189: 254–59.
17. Simonsen C, Sundet K, Vaskinn A, Birkenaes AB, Engh JA, Hansen CF, et al. Neurocognitive profiles in bipolar I and bipolar II disorder: differences in pattern and magnitude of dysfunction. Bipolar Disord 2008; 10: 245-55.
18. Summers M, Papadopoulou K, Bruno S. Bipolar I and bipolar II disorder: cognition and emotion processing. Psychol Med 2006; 36: 1799-1809.
19. Reichenberg A, Weiser M, Rabinobitz J, Caspi A, Schmeidler J, Mark M, et al. A population-based cohort study of premorbid intellectual, language and behavioral functioning in patients with schizophrenia, schizoaffective disorder and non-psychotic bipolar disorder. Am J Psychiatry 2002; 159: 2027-35.
20. Tiihonen J, Haukka J, Henriksson M, Cannon M, Kieseppä T, Laaksonen I, et al.

Pre-morbid intellectual functioning in bipolar disorder and schizophrenia: results from cohort study of a male conscripts. Am J Psychiatry 2005; 162:1904-10.
21. Zanelli J, Reichenberg A, Morgan K, Fearon P, Kravariti E, Dazzan P, et al. Specific and generalized neuropsychological deficits: a comparison of patients with various first-episode psychosis presentations. Am J Psychiatry 2010; 167: 78–85.
22. Mur M, Portella MJ, Martinez-Aran A, Pifarre J, Vieta E. Long-term stability of cognitive impairment in bipolar disorder: a 2-year follow-up study of lithium-treated Euthymic bipolar patients. J Clin Psychiatry 2008; 69: 712-19.
23. Balanza-Martinez V, Tabares-Seisdedos R, Selva-Vera G, Martínez-Arán A, Torrent C, Salazar-Fraile J, et al. Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: 3-year follow-up study. Psychother Psychosom 2005; 74: 113-19.
24. Robinson LJ, Ferrier IN. Evolution of cognitive impairment in bipolar disorder: a systematic review of cross-sectional evidence. Bipolar Disord 2006; 8: 103-16.
25. Arts B, Jabben N, Krabbendam L, van Os J. A 2-year naturalistic study on cognitive functioning in bipolar disorder. Acta Psych Scand 2011; 123: 190-205.
26. Malhi GS, Ivanovski B, Hadzi-Pavlovic D, Mitchell PB, Vieta E, Sachdev P. Neuropsychological deficits and functional impairment in bipolar depression, hypomania and euthymia. Bipolar Disord 2007; 9: 114-25.
27. Clark L, Goodwin GM. State and trait-related deficits in sustained attention in bipolar disorder. Eur Arch Psychiatry Clin Neurosci 2004; 254: 61-8.
28. Quraishi S, Frangou S. Neuropsychology of bipolar disorder:a review. J Affect Disord 2002; 72: 209-26.
29. Latalova K, Prasko J, Diveky T, Velartova H. Cognitive impairment in bipolar disorder. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011; 155:19-26.
30. Rubinsztein JS, Micahel A, Paykel ES, Sahakian BJ. Cognitive impairment in remission in bipolar affective disorder. Psychol Med 2000; 30: 1025-36.
31. Liu SK, Chiu CH, Chang CJ, Hwang TJ, Hwu HG, Chen WJ. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. Am J Psychiatry 2002; 159: 975-82.
32. Clark L, Kempton MJ, Scarna A , Grasby PM, Goodwin GM. Sustained attention deficit confirmed in euthymic bipolar disorder but not in first degree relatives of bipolar patients or euthymic unipolar depression. Biol Psychiatry 2005; 57: 183-87.
33. Ferrier IN, Chowdury R, Thompson JM, Watson S, Young AH. Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. Bipolar Disord 2004; 6: 319-22.
34. Frangou S, Haldane M, Roddy M, Kumari V. Evidence for deficits in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. Biol Psychiatry 2005; 58: 838-39.
35. Gourovitch ML, Torrey EF, Gold JM, Randolph C, Weinberger DR, Goldberg TE. Neuropsychological performance of monozygotic twins discordant for bipolar disorder. Biol Psychiatry 1999; 45: 639-46.
36. Kieseppa T, Tuulio-Henriksson A, Haukka J, Van Erp T, Glahn D, Cannon TD, et al. Memory and verbal learning functions in

twins with bipolar-I disorder and the role of information processing speed. Psychol Med 2005; 35: 205-15.
37. Christensen MV, Kyvik KO, Kessing LV. Cognitive function in unaffected twins discordant for affective disorder. Psychol Med 2006; 36: 1119-29.
38. Taj M, Padmavati R. Neuropsychological impairment in bipolar affective disorder. Indian J Psychiatry 2005; 47: 48-50.
39. Trivedi JK, Dhyani M, Sharma S, Sinha PK, Singh AP, Tandon R. Cognitive functions in euthymic state of bipolar disorder: An Indian study. Cogn Neuropsychiatry 2008; 13: 135-47.
40. Pattanayak RD, Sagar R, Mehta M. Neuropsychological performance in euthymic Indian Patients with Bipolar Disorder-type I: Relationship to quality of life and global functioning. Psychiatry Clin Neurosci 2011, under publication.
41. Goswami U, Sharma A, Khastigir U, Ferrier IN, Young AH, Gallagher P, et al. Neuropsychological dysfunction, soft neurological signs and social disability in euthymic patients with bipolar disorder. Br J Psychiatry. 2006; 188: 366-73.
42. Nehra R, Chakrabarti S, Pradhan BK, Khehra N.Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. J Affect Disord. 2006; 93: 185-92.
43. Trivedi JK, Goel D, Sharma S, Singh AP, Sinha PK, Tandon R. Cognitive functions in stable schizophrenia and euthymic state of bipolar disorder. Indian J Med Res 2007; 126: 433-9.
44. Pradhan BK, Chakraborti S, Nehra R, Mankotia A. Cognitive functions in bipolar affective disorder and schizophrenia: comparison. Psychiatry Clin Neurosci 2008; 62: 515-25.
45. Goswami U, Sharma A, Varma A, Gulrajani C, Ferrier IN, Young AH, et al.The neurocognitive performance of drug-free and medicated euthymic bipolar patients do not differ. Acta Psychiatr Scand. 2009; 120: 456-63.
46. Kulkarni S, Jain S, Janardhan Reddy YC, Kumar KJ, Kandavel T. Impairment of verbal learning and memory and executive function in unaffected siblings of probands with bipolar disorder. Bipolar Disord. 2010; 12: 647-56.
47. Trivedi JK, Goel D, Dhyani M, Sharma S, Sinha PK, Singh AP, Tandon R. Neurocognition in first-degree healthy relatives (siblings) of bipolar affective disorder patients. Psychiatry Clin Neurosci 2008; 62:190-6.
48. Manove E. Levy B. Cognitive impairment in bipolar disorder: An overview. Postgraduate Medicine 2010; 122: 7-16.
49. Kolur US, Reddy YC, John JP, Kandavel T, Jain S. Sustained attention and executive functions in euthymic young people with bipolar disorder. Br J Psychiatry 2006; 189: 453-58.
50. Pavuluri MN, West A, Hill SK, Jindal K, Sweeney JA. Neurocognitive function in pediatric bipolar disorder: 3-year follow-up shows cognitive development lagging behind healthy youths. J Am Acad Child Adolesc Psychiatry 2009; 48: 299–307.
51. Vita A, De Peri L, Sacchetti E. Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. Bipolar Disord 2009; 11: 807–14.
52. Terry J, Lopez-Larson M, Frazier JA. Magnetic resonance imaging studies in early onset bipolar disorder: an updated review. Child Adolesc Psychiatr Clin N Am. 2009;

18: 421-39.
53. Zimmerman ME, DelBello MP, Getz GE, Shear PK, Strakowski SM. Anterior cingulate subregion volumes and executive function in bipolar disorder. Bipolar Disord 2006; 8: 281-88.
54. Lopez-Jaramillo C, Lopera-Vasquez J, Ospina-Duque, Garcia J, Gallo A, Cortez V, et al. Lithium treatment effects on the neuropsychological functioning of patients with bipolar I disorder. J Clin Psychiatry 2010; 71: 1055-60.
55. Finkel D, Pedersen NL, McGue M, McClearn GE. Heritability of cognitive abilities in adult twins: comparison of Minnesota and Swedish data. Behav Genet 1995; 25: 421–31.

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Dr Raman Deep Pattanayak, Senior Research Associate (CSIR-pool)
Dr Rajesh Sagar, Additional Professor
Dr Manju Mehta, Professor
Department of Psychiatry, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr Rajesh Sagar, Additional Professor, Department of Psychiatry, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India-110029. Email: rajeshsagar@ rediffmail.com