

# Neurological Abnormalities in Drug-free and Drug-treated Patients with Bipolar Affective Disorder

SK Praharaj, D Ram, M Arora

## Abstract

**Objective:** To assess the effect of medication on neurological abnormalities in patients with bipolar affective disorder.

**Patients and Methods:** Neurological abnormalities were examined in 30 drug-free patients and 30 drug-treated patients meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition diagnostic criteria for bipolar affective disorder, and 20 age- and sex-matched controls, using the Extended Standard Neurological Assessment Instrument. Mania and depression were assessed using the Young Mania Rating Scale and the Hamilton Rating Scale for Depression, respectively. Side effects of medications were assessed using the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale.

**Results:** Patients with bipolar affective disorder had higher mean total scores on the Extended Standard Neurological Assessment Instrument (drug-free group  $22.83 \pm 11.04$ , drug-treated group  $22.00 \pm 10.23$ ) than controls, who did not score on any items of the neurological battery. There was a significant excess of hard signs and involuntary movements in the drug-treated group compared with the drug-free group, and a significant positive correlation between hard signs and the involuntary movements score and the neurological subscore on Udvalg for Kliniske Undersøgelser Side Effect Rating Scale in the drug-treated group.

**Conclusion:** The presence of neurological signs in drug-free patients with bipolar affective disorder suggests that neurological abnormalities may occur independently of medication effects. Side effects of drug treatment for bipolar affective disorder may contribute to the prevalence of neurological abnormalities in this patient population.

**Key words:** Bipolar disorder, Dyskinesia, drug-induced, Neurologic manifestations

## Introduction

There has been a steady increase in interest and appreciation of the biological underpinnings of mood disorders. Bipolar disorder appears to be related to anatomic abnormalities in the medial temporal lobe, in particular the amygdala, prefrontal cortex and cerebellum.<sup>1</sup> Recent magnetic resonance imaging findings support a neurodevelopmental etiology for bipolar affective disorder, at least in a subgroup of patients, as for schizophrenia. The frequency of medial temporal lobe

(hippocampus/amygdala complex) hypoplasia noted in patients with bipolar affective disorder was similar to that seen in schizophrenia, and correlated with the degree of cognitive impairment.<sup>2</sup>

A meta-analysis by Videbech<sup>3</sup> showed an increased ventricle/brain ratio and other signs of cerebral atrophy, as well as an increased frequency of signal hyperintensity, in the frontal lobes and basal ganglia of patients with bipolar affective disorder. Shioiri et al<sup>4</sup> reported a higher incidence of cavum septum pellucidum in subjects with bipolar affective disorder than controls, but lower than in subjects with schizophrenia.

Neurological soft signs (NSS) have been reported in minimal brain dysfunction,<sup>5</sup> emotionally unstable character,<sup>6</sup> heavy polydrug users,<sup>7</sup> borderline personality disorder,<sup>8</sup> obsessive compulsive disorder,<sup>9</sup> and consistently in individuals with schizophrenia.<sup>10,11</sup> Nasrallah et al<sup>12</sup> found that NSS are as common in individuals with mania as in those with schizophrenia. An excess of neurological signs in adults with bipolar affective disorder has also been reported by other researchers.<sup>13-15</sup> Basu et al<sup>16</sup> reported similar findings in adolescents with mania. These soft signs are thought to reflect

*Dr Samir Kumar Praharaj, MBBS, DPM, Resident, Central Institute of Psychiatry, Kanke, Ranchi, 834 006, India.*

*Dr Daya Ram, MBBS, MD, Professor of Psychiatry, Central Institute of Psychiatry, Kanke, Ranchi, 834 006, India.*

*Dr Manu Arora, MBBS, MD, DPM, Senior Resident, Central Institute of Psychiatry, Kanke, Ranchi, 834 006, India.*

**Address for correspondence:** Dr Samir Kumar Praharaj, Central Institute of Psychiatry, Kanke, Ranchi, 834 006, India.

Tel: (91 651) 223 1689;

E-mail: samirpsyche@yahoo.co.in

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diffuse brain dysfunction. However, it has been suggested that although diffuse, NSS may reflect selective dysfunction in areas of motor coordination, integrative sensory function, and complex motor task coordination.<sup>17</sup>

One area of interest has been the role of medication in the expression of neurological abnormalities. Although few studies have been able to exclude the influence of medication in the appearance of neurological abnormalities,<sup>6,18</sup> a comprehensive review by Heinrichs and Buchanan<sup>17</sup> concluded that medications do not seem to alter neurological signs in most cases of schizophrenia. Dazzan and Murray<sup>19</sup> completed a meta-analysis and reported an excess of NSS in patients with first-episode psychosis, particularly in the areas of motor coordination and sequencing, sensory integration and developmental reflexes. This was thought to be associated with a specific laterality pattern. Wong et al<sup>20</sup> reported that the use of neuroleptics increased soft signs in patients, while Mukherjee et al<sup>13</sup> found a strong correlation between the duration of cumulative neuroleptic exposure and the presence of neurological abnormalities in patients with bipolar affective disorder. A further study<sup>21</sup> showed that patients with bipolar disorder receiving treatment with antipsychotic agents performed poorly on cognitive measures compared with a control group. However, most studies failed to control for medication status in the study design.

This study was designed to gather further information on the clinical, sociodemographic, psychopathological correlates and the effect of medications on neurological abnormalities in bipolar affective disorder.

## Patients and Methods

The study was a cross-sectional, hospital-based study, conducted at the Central Institute of Psychiatry, Ranchi, India. Sixty patients with bipolar affective disorder (30 drug-free, 30 drug-treated) and 20 age- and sex-matched controls were recruited for the study. Inclusion criteria for the patient groups were: inpatients or outpatients of either sex; aged between 18-55 years; meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria for bipolar affective disorder; with a current episode of mania or depression; able to cooperate with testing. Drug-free was defined as not having been taking any psychotropic medications in the past month. Drug-treated was defined as on psychotropic medication for at least one month. Patients with organic brain syndrome, any other major psychiatric illness, mental retardation, or who had received electroconvulsive therapy within the previous 6 months were excluded. Control subjects were workers at the Central Institute of Psychiatry. Exclusion criteria for the control group included a history of psychosis, affective disorder, significant head injury, any major neurological disorder, epilepsy or major physical illness. A history of substance abuse or dependence, or a family history of major mental disorder were further exclusion criteria for this group.

The severity of illness was assessed using the 11-item, clinician-administered Young Mania Rating Scale (YMRS)<sup>22</sup>

and the 24-item clinician-administered Hamilton Depression Rating Scale (HDRS),<sup>23</sup> both of which have good psychometric properties. A general health questionnaire (GHQ-5)<sup>24</sup> was used to screen for psychiatric morbidity in the control group. The 5-item GHQ-5 (containing items 14, 38, 42, 49 and 54 of the original GHQ and designed by the original authors) has been reported to have a sensitivity of 86% and specificity of 89%.<sup>24</sup>

The Extended Standard Neurological Assessment Instrument (ESNAI)<sup>25</sup> was used to assess neurological abnormalities. The ESNAI is a comprehensive battery for this purpose, consisting of 44 items over four domains (motor 26 items, cognitive function 6 items, reflexes 7 items, sensory 5 items), and includes both hard and soft neurological signs. In a previous study, inter-rater reliability for the neurological assessment between the examiner and two other physicians was (intra-class correlation) 0.87 and 0.97, respectively.<sup>25</sup> A few minor modifications were made to make items appropriate for Indian patients (eg, for item 20, tying a rope for males or tying hair for females instead of tying a shoelace as most patients did not wear shoes). The Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale<sup>26</sup> was used to assess side effects due to psychotropic medications.

## Data Analysis

Data were analysed using the statistical software package Statistical Package for the Social Sciences 10.1. Control subjects were excluded from analysis as none had scored on any items of the scales used. Differences within the patient group in sociodemographic variables, and neurological scores between drug-free and drug-treated subgroups were analysed using the Chi-squared test and the independent samples *t* test, respectively. Pearson correlation coefficients were calculated between clinical variables, the YMRS score and UKU scores, and neurological scores. Analysis of variance with post hoc Bonferonni testing was used to assess differences between the various drug-treated groups on the neurological scores. Discriminant analysis was completed to examine whether neurological scores were able to classify the different patient subgroups.

## Results

Characteristics of the study participants and differences between the groups are shown in Table 1. The mean  $\pm$  SD age of the patients was  $32.96 \pm 9.11$  years in the drug-free group and  $28.83 \pm 9.10$  years in the drug-treated group, which was similar to controls ( $28.25 \pm 7.38$  years). There was a high representation of males (76.7%) overall but the composition of the groups was similar. The mean age of onset of illness overall was  $26 \pm 8.64$  years (range 13-50), being comparable in the drug-free ( $28.33 \pm 9.48$  years) and the drug-treated groups ( $23.76 \pm 6.44$ ). The mean number of bipolar episodes was  $2.62 \pm 2.04$  (range 1-10). There was a significant difference ( $p < 0.001$ ) in the mean YMRS scores between the drug-free and drug-treated groups.

**Table 1. Characteristics of the study groups.**

Variable	Group			Statistical test	p Value
	Drug-free Mean $\pm$ SD (%)	Drug-treated Mean $\pm$ SD (%)	Normal Mean $\pm$ SD (%)		
Mean age (years)	32.96 $\pm$ 9.11	28.83 $\pm$ 9.10	28.25 $\pm$ 7.38	F = 2.380	0.099
Sex					
Men	21 (70.0)	25 (83.3)	16 (80)	$\chi^2 = 1.625$	0.444
Women	9 (30.0)	5 (16.7)	4 (20)		
Socioeconomic status					
Middle	25 (83.3)	28 (93.3)	19 (95)	$\chi^2 = 2.407$	0.3
Lower	5 (16.7)	2 (6.7)	1 (5)		
Residence					
Rural	19 (63.3)	21 (70)	4 (20)	$\chi^2 = 13.468$	< 0.001
Urban	11 (36.7)	9 (30)	16 (80)		
Clinical					
Age at onset (years)	28.23 $\pm$ 9.48	23.76 $\pm$ 6.44	-	$t = 2.134$	< 0.05
Current episode					
Mania	28 (93.3)	30 (100)	-	$\chi^2 = 0.517$	0.472
Depression	2 (6.7)	0			
Young Mania Rating Scale score	27.10 $\pm$ 8.45	17.46 $\pm$ 7.39	-	$t = 4.030$	< 0.001

**Table 2. Comparison of neurological abnormalities between the drug-free and drug-treated group.**

Neurological signs	Group		t	p Value
	Drug-free n = 30 (mean $\pm$ SD)	Drug-treated n = 30 (mean $\pm$ SD)		
Total score	22.83 $\pm$ 11.04	22.00 $\pm$ 10.23	0.303	0.763
Filtered score	22.20 $\pm$ 10.67	19.80 $\pm$ 9.75	0.909	0.367
Soft signs	18.43 $\pm$ 9.20	15.70 $\pm$ 7.87	1.236	0.221
Hard signs	4.40 $\pm$ 3.23	6.30 $\pm$ 3.57	2.159	< 0.05
Filtered hard signs	3.66 $\pm$ 2.60	4.10 $\pm$ 2.70	0.632	0.530
Motor coordination	5.00 $\pm$ 3.04	4.86 $\pm$ 3.36	0.161	0.873
Involuntary movements	0.63 $\pm$ 1.09	2.20 $\pm$ 1.84	3.995	< 0.001
Mirror movements	0.66 $\pm$ 0.99	0.50 $\pm$ 1.10	0.614	0.542
Cranial nerves	0.23 $\pm$ 0.54	0.30 $\pm$ 0.46	0.532	0.597
Total motor	6.53 $\pm$ 4.19	7.80 $\pm$ 5.19	1.039	0.303
Cognitive	8.33 $\pm$ 3.63	6.33 $\pm$ 3.55	1.831	0.072
Reflexes	0.86 $\pm$ 2.92	1.00 $\pm$ 0.78	0.241	0.810
Sensory	7.00 $\pm$ 3.76	6.50 $\pm$ 3.52	0.532	0.597
Left abnormality score	3.43 $\pm$ 2.83	4.10 $\pm$ 2.42	0.978	0.332
Right abnormality score	3.33 $\pm$ 2.41	3.83 $\pm$ 2.43	0.799	0.428

The mean total score on the neurological assessment battery was similar for both patient groups, with a mean of 22.83  $\pm$  11.04 for the drug-free group and 22.00  $\pm$  10.23 for the drug-treated group. There was a significant excess of hard signs ( $p < 0.05$ ) and involuntary movement scores ( $p < 0.001$ ) in the drug-treated group compared with the drug-free group (Table 2). In terms of educational status, patients who had less than 10 years of formal education had significantly higher mean scores ( $p < 0.01$ ) in total score

( $t = 4.041$ ), filtered score ( $t = 4.195$ ), soft signs ( $t = 4.203$ ), filtered hard signs ( $t = 3.222$ ), motor coordination ( $t = 3.547$ ), total motor ( $t = 2.930$ ), cognitive score ( $t = 4.593$ ) sensory ( $t = 3.537$ ), left abnormality score ( $t = 3.139$ ) and right abnormality score ( $t = 2.686$ ), and significantly higher mean scores ( $p < 0.05$ ) in hard signs ( $t = 2.506$ ), than those with 10 or more years of formal education.

Significantly higher mean scores ( $p < 0.01$ ) were also seen in residents of rural areas than those of urban areas in

**Table 3. Comparison of neurological signs in subgroups by treatment agents.**

Neurological signs	Group			F	p Value
	Antipsychotics n = 11 Mean ± SD	Mood stabilisers n = 3 Mean ± SD	Antipsychotics + mood stabilisers n = 16 Mean ± SD		
Total score	18.18 ± 7.54	29.66 ± 5.77	23.18 ± 11.66	1.812	0.183
Filtered score	16.18 ± 7.96	27.66 ± 4.16	20.81 ± 10.78	1.936	0.164
Soft signs	12.54 ± 6.50	21.33 ± 5.03	16.81 ± 8.56	1.925	0.165
Hard signs	5.63 ± 3.32	8.33 ± 2.30	6.37 ± 3.93	0.663	0.523
Filtered hard signs	3.63 ± 2.65	6.33 ± 1.15	4.00 ± 2.85	1.209	0.31
Motor coordination	4.36 ± 3.00	6.00 ± 3.60	5.00 ± 3.68	0.291	0.749
Involuntary movements	2.00 ± 1.78	2.00 ± 2.00	2.37 ± 1.96	0.145	0.866
Mirror movements	0.18 ± 0.40	1.00 ± 1.00	0.62 ± 1.40	0.855	0.437
Cranial nerves	0.18 ± 0.40	0.33 ± 0.57	0.37 ± 0.50	0.551	0.583
Total motor	6.72 ± 3.69	9.33 ± 6.65	8.25 ± 5.97	0.408	0.669
Cognitive	6.00 ± 3.52	10.33 ± 3.21	6.37 ± 3.42	1.961	0.160
Reflexes	1.00 ± 0.77	0.66 ± 0.57	1.06 ± 0.85	0.304	0.741
Sensory*	4.45 ± 3.04	9.33 ± 3.21	7.37 ± 3.30	4.012	< 0.05
Left abnormality score	3.00 ± 1.78	5.00 ± 1.73	4.68 ± 2.72	1.921	0.166
Right abnormality score	3.00 ± 1.34	4.66 ± 2.08	4.25 ± 2.97	1.057	0.361

\* Significant group difference between: patients on antipsychotics and those on mood stabilisers; and between patients on antipsychotics and those on antipsychotics plus mood stabilisers.

the total score ( $t = 4.249$ ), filtered score ( $t = 4.060$ ), soft signs ( $t = 4.034$ ), hard signs ( $t = 3.550$ ), filtered hard signs (2.971), motor coordination scores ( $t = 4.111$ ), involuntary movements score ( $t = 2.832$ ), cranial nerve score ( $t = 3.432$ ), total motor score ( $t = 4.391$ ), cognitive ( $t = 0.119$ ), sensory ( $t = 4.365$ ), left abnormality score ( $t = 3.186$ ) and right abnormality score ( $t = 3.910$ ).

Of the drug-treated group ( $n = 30$ ), 36.6% had been prescribed an antipsychotic agent only, 10% had been prescribed a mood stabiliser only, and the remainder (53.4%) had been prescribed both an antipsychotic agent and a mood stabiliser. No significant differences were seen between these three groups on the neurological signs scores, with the exception of the sensory domain scores (Table 3). Significantly higher scores were found in the groups receiving mood stabilisers only, and mood stabilisers plus antipsychotic, compared to the group receiving antipsychotics only ( $F = 4.012$ ,  $p < 0.05$ ).

The neurological subscore of the UKU scale correlated positively with total score, hard signs, involuntary movements, total motor score, left and right abnormality score ( $p < 0.01$ ) and with filtered score, filtered hard signs, motor coordination, and mirror movements ( $p < 0.05$ ) [Table 4]. The autonomic and other subscores of the UKU scale showed no correlation with any of the neurological scores. Current age and number of episodes did not correlate significantly with any of the neurological signs. Age of onset of illness correlated negatively with the sensory domain of the neurological battery. The YMRS scores correlated positively with total score ( $p < 0.05$ ) and with filtered score, soft signs,

motor coordination and cognitive scores ( $p < 0.01$ ), and were negatively correlated with involuntary movements ( $p < 0.05$ ) level. The correlation between the HDRS score and the neurological scores could not be calculated because of the small number of patients with depressive episodes in the sample.

Discriminant analysis was completed for the neurological scores in the sample groups. Discriminant analysis of all scores together was better able to classify between groups than individual scores. Approximately two-thirds of drug-free patients were correctly classified as drug-free and approximately two-thirds of drug-treated patients were correctly classified as drug-treated, whereas all controls were correctly classified. Overall, 75 % of the sample were correctly classified.

## Discussion

The main objective of this study was to determine the effect of medication on neurological signs in patients with bipolar affective disorder. In the present study, patients with bipolar affective disorder were found to have higher neurological scores than normal controls, who did not score on any of the items of the neurological battery. A similar excess of neurological signs in patients with bipolar affective disorder has been observed in previous studies.<sup>12-16,27-29</sup> The presence of neurological abnormalities in patients with bipolar disorder not currently on drug treatment indicates that the abnormalities are not merely an epiphenomenon of treatment.

**Table 4. Correlation between Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale score, clinical variables and neurological signs.**

Neurological signs	UKU Side Effect Rating Scale score					Age	Age of onset	Young Mania Rating Scale score
	Total score	Psychic	Neurological	Autonomic	Others			
Total score	0.315	0.245	0.471 <sup>†</sup>	0.310	0.203	-0.125	-0.139	0.296*
Filtered score	0.320	0.283	0.364*	0.339	0.178	-0.105	-0.123	0.358 <sup>†</sup>
Soft signs	0.258	0.205	0.305	0.323	0.151	-0.094	-0.143	0.345 <sup>†</sup>
Hard signs	0.333	0.249	0.677 <sup>†</sup>	0.176	0.248	-0.144	-0.068	0.038
Filtered hard signs	0.401*	0.422*	0.427*	0.283	0.202	-0.100	0.019	0.231
Motor coordination	0.281	0.267	0.418*	0.339	0.289	-0.046	0.006	0.344 <sup>†</sup>
Involuntary movements	0.055	-0.138	0.685 <sup>†</sup>	-0.075	0.184	-0.145	-0.124	-0.296*
Mirror movements	0.230	0.133	0.363*	0.235	0.256	-0.055	-0.068	0.163
Cranial nerves	0.152	0.156	0.097	0.359	0.284	0.040	-0.080	0.175
Total motor	0.270	0.178	0.590 <sup>†</sup>	0.276	0.334	-0.087	-0.061	0.171
Cognitive	0.280	0.329	0.258	0.271	0.073	-0.144	-0.113	0.435 <sup>†</sup>
Reflexes	0.125	0.086	0.177	0.073	0.000	0.008	0.102	0.082
Sensory	0.215	0.116	0.183	0.205	0.027	-0.110	-0.282*	0.095
Left abnormality score	0.319	0.219	0.491 <sup>†</sup>	0.316	0.148	-0.187	-0.233	0.080
Right abnormality score	0.188	0.036	0.595 <sup>†</sup>	0.150	0.245	-0.100	-0.092	0.154

\* Correlation significant at 0.05 level.

† Correlation significant at 0.01 level.

It has been argued previously that specific neurological signs could be linked to medication effects.<sup>6</sup> In the present study, significantly higher scores in terms of hard signs and involuntary movements were found in the patient group receiving drug treatment, compared with patients not taking medication, indicating that these neurological features might be an effect of medication. The items in the involuntary movement subscales (intention tremor, choreiform and athetoid movements, postural and resting tremor), occur commonly as side effects of the drugs, and appear to explain the excess of involuntary movement scores in the drug-treated patients.

A significant positive correlation between scores on hard signs and involuntary movements, and the neurological subscore on the UKU scale in the drug-treated patients further indicates that drugs might be partially responsible for the presence of neurological abnormalities. A similar excess of neurological signs in drug-treated patients has been observed in earlier studies.<sup>11,13,18</sup> However, the presence of neurological signs in patients not currently on medication regimens could support the presence of neurological abnormalities in bipolar affective disorder independent of medication effects.

In the drug-treated groups, no significant differences in neurological signs were seen between patients receiving different medications, with the exception of the sensory domain score. A significantly higher score was found in the patients receiving mood stabilisers only. However, as there were only 3 patients in the mood stabiliser-only group, this finding may be spurious.

The significant positive correlation of neurological scores including total score, filtered score, soft signs, motor coordination and cognitive domain with the YMRS score implies that neurological abnormalities increase with the severity of mania. This is in keeping with findings reported by Basu et al<sup>16</sup> The involuntary movements subscore correlated negatively with the YMRS score, suggesting that these test items are not associated with severity of mania, and may represent medication side effects.

In the present study, no significant association was found between age and neurological signs, in agreement with a number of previous studies,<sup>15,30,31</sup> but contrasting with Torrey,<sup>32</sup> who reported a general association between neurological impairment and increasing age. No significant relationship was found between neurological scores and sex or socioeconomic status. This is in contrast to some studies in which significant differences were found according to these demographic variables.<sup>11,28,33,34</sup> In the present study, the patients who had less than 10 years of formal education had significantly higher neurological abnormalities scores than those with a higher educational level. It could be argued that lower education is a proxy index of poor socioeconomic status which can make individuals more prone to insults such as infections and deficiencies during early childhood.<sup>34</sup> This seems plausible, at least in developing countries.<sup>35</sup> In this study, it was found that residents of rural areas also had significantly higher neurological scores than the residents of urban areas, which could be explained by extending the above argument.

The reported presence of neurological signs in patients with bipolar affective disorder who have not been exposed

to psychotropic medication is thought to reflect attentional deficits.<sup>31</sup> Basu et al<sup>16</sup> reported that performance on the rhythm tapping test and the go-no-go test, measures of attention, concentration and alertness, were impaired in majority of patients during a manic episode and had improved significantly during a second assessment four weeks later. Attention, concentration and alertness are known to be impaired during the height of a manic episode.<sup>36</sup> In the present study, cognitive items of the neurological assessment instrument, gaze persistence and imaginary acts were impaired in the majority of the drug-free patients compared with the drug-treated group. The drug-free and drug-treated groups differed significantly on YMRS scoring, which points to the reduction of symptoms with treatment.

Another point of discussion regarding the neurological signs is the so-called state versus trait effect. McKay et al<sup>37</sup> reported enduring neuropsychological deficits in patients with bipolar affective disorder, suggesting a trait effect, at least in a subgroup of patients. Basu et al<sup>16</sup> in contrast, reported a decrease in neurological signs in manic patients with resolution of the manic episode.

In addition to a relatively small sample size, a limitation of this study was that the sample consisted predominantly of patients with mania. Patients with depressive episodes were under-represented. Furthermore, the neurological assessment battery was administered by one rater who was blind to neither the diagnosis nor the medication status of the patients.

There is wide variation in the items included as neurological abnormalities in the neurological assessment instruments used by previous studies, making comparison across studies difficult. The results of the discriminant analysis showed that the neurological assessment scale was poor at classifying patient groups, though it did correctly identify controls. There is a need for a universally accepted, structured and reliable procedure for rating neurological signs in bipolar affective disorder to make comparison across studies meaningful. The ideal procedure would not include items known to be associated with medication, such as tremor and other abnormal involuntary movements.

Despite methodological limitations, the study adds to the evidence for a higher rate of neurological abnormalities in bipolar disorder, which is consistent and compelling. These abnormalities do not appear to be random but rather are concentrated in motor, cognitive and sensory domains. These findings point toward deficits in the frontal and parietal lobe, in contrast to the report by Cherian and Kuruvilla,<sup>14</sup> who found that most soft signs in patients with bipolar disorder are related to temporal and parietal lobe function. The left abnormality scores were higher than the right abnormality scores in both the drug-free and drug-treated patients, suggesting a laterality effect. Similar results were reported by Niethammer et al,<sup>38</sup> in contrast to higher right-sided scores observed in other studies.<sup>32,39</sup> The accumulating body of data make it difficult to interpret the neurological abnormalities as simply representing nonspecific indicators of organic brain dysfunction. In contrast, the neurological

abnormalities appear to reflect pathological changes in neural systems that are responsible not only for balance, motor coordination and sequencing, and sensory integration, but also seem to have a vital role in (ab)normal cognition and behavior.<sup>40</sup>

A further reason for studying neurological abnormalities in patients with bipolar disorder is that these patients may have a distinct variant of illness and may be good candidates for valproate therapy.<sup>41</sup> The presence of neurological abnormalities has also been noted to be associated with a higher relapse rate during follow-up.<sup>13</sup> Compared to other techniques for evaluating neurological aspects of bipolar disorder, the study of neurological signs is inexpensive and can be readily employed with large samples. Further studies are required using neurological assessment batteries along with neuroimaging studies to support existing findings on the relationship between bipolar affective disorder and neurological abnormalities.

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