The Impact of Homocysteine Levels on Cognition in Euthymic Bipolar Patients: A Cross-Sectional Study

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Objective: Bipolar disorder is associated with cognitive impairment. High homocysteine levels seem to have a negative impact on cognition in the elderly. The aim of the present study was to investigate the potential relationship of elevated homocysteine levels and cognitive impairment in bipolar patients.

Method: Cognitive functioning of DSM-IV bipolar disorder patients who were euthymic (Hamilton Rating Scale for Depression score ≤ 5 and Young Mania Rating Scale score ≤ 5) and healthy controls was assessed with the revised Wechsler Adult Intelligence Scale Information Subtest, the Wechsler Adult Intelligence Scale III Letter-Number Sequencing Subtest, the Trail Making Test, and the Repeatable Battery for the Assessment of Neuropsychological Status Form A to examine premorbid IQ, information processing speed, working memory, verbal learning, visuospatial/constructional abilities, delayed memory, and executive functions. Total homocysteine plasma concentration was measured by using high-performance liquid chromatography. Multivariate analyses of variance and multiple regression analyses were conducted to examine group differences and possible associations between cognitive functioning and homocysteine level. The study was conducted from 2002 through 2006.

Results: Seventy-five euthymic bipolar patients and 42 healthy controls participated in the study. Patients performed significantly worse than controls in all cognitive domains tested (Pillai Spur: $F = 3.32$, $p = .038$) except premorbid IQ ($p = .068$). The mean ± SD homocysteine levels were 10.2 ± 3.2 μM/L for patients and 8.9 ± 2.8 μM/L for controls ($p = .036$). Stepwise regression analyses revealed a significant and independent association of homocysteine levels with verbal learning ($p = .002$), delayed memory ($p = .030$), and executive function ($p = .011$) in the patient group. About 11% of the variance was explained by only the homocysteine level.

Conclusion: Elevated homocysteine levels may have a negative impact on verbal learning, delayed memory, and executive function in euthymic bipolar patients, but further studies are warranted.

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Cognitive impairment appears to be present in bipolar disorder even during euthymia[1–3] and may account for functional and occupational disability.[4,5] While imaging studies suggest structural, neurochemical, and functional abnormalities in bipolar disorder,[6] the pathophysiology of these deficits has still not been elucidated yet.

In the last few years, there has been growing evidence that elevated plasma homocysteine levels are a risk factor for cognitive impairment and dementia in the general population, and they are associated with white matter lesions and silent brain infarctions in elderly people.[7–15] Information processing speed,[16] verbal as well as nonverbal memory,[16,17] visuospatial/constructional abilities,[18] and reasoning[19] are the cognitive domains that seem to be most impaired. In addition, a recent randomized double-blind, placebo-controlled trial demonstrated that

lowering homocysteine levels by taking folic acid is associated with positive effects on memory, information processing speed, and sensorimotor speed in healthy elderly subjects.[20]

Elevated homocysteine levels have also been reported in some but not all studies of other psychiatric disorders, such as schizophrenia[21–23] and depression.[24–29] Furthermore, a genetic polymorphism of the methylenetetrahydrofolate reductase gene leading to increased homocysteine levels seems to be associated with unipolar as well as bipolar disorder.[27] Another study found larger functional deterioration in bipolar patients with elevated homocysteine levels compared to those with plasma levels in the normal range.[30]

Homocysteine, a sulfur-containing amino acid that is part of the methionine metabolism, could adversely affect cognitive function in several ways. For example, it could represent a marker for insufficient supply of B vitamins due to nutritional deficiency and/or reduced glomerular filtration rate.[27] In addition, high homocysteine levels are a recognized cardiovascular risk factor and may contribute to cognitive impairment by causing silent brain infarction.[11,31] Furthermore, oxidized forms of homocysteine, such as homocysteic acid, are potent neurotoxic agents leading to apoptosis and leukaraiosis.[32] It has also been suggested that disturbances in methylation pathways, including methylation of DNA, neurotransmitters, and phospholipids, have negative consequences for the proper function of cerebral tissue.[32] For example, Kruman et al.[33] could demonstrate that homocysteine elicits DNA damage response in neurons and promotes apoptosis and hypersensitivity to excitotoxicity. Moreover, the same group showed that homocysteine and folate deficiency impair DNA repair in neurons, sensitizing them to oxidative damage.[34] Folate deficiency in particular seems to inhibit proliferation of neuronal progenitor cells in the adult brain and thereby adversely affects neurogenesis.[35]

It therefore seemed reasonable to investigate whether cognitive impairment in euthymic bipolar patients might be associated with elevated plasma homocysteine levels and to explore which cognitive domains might be affected the most.

Our hypothesis was that patients with bipolar disorder will have higher plasma homocysteine levels than healthy controls and that these higher levels would negatively correlate with cognitive function, especially with information processing speed, visuospatial/constructional abilities, delayed memory, and executive functions.

METHOD

Subjects

Patients participating in the present study were enrolled from the Stanley Foundation Bipolar Network at the Bipolar Outpatient Center of the Psychiatric Hospital of the Ludwig-Maximilians-University, Munich, Germany. Patients participating in this network were seen monthly by senior psychiatrists and had to undergo extensive psychopathological ratings and life charting (for further details, see Dittmann et al.[36] and Leverich and Post[37]).

To be enrolled in the present study, patients had to be diagnosed with bipolar I or II disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[38] had to be euthymic (Hamilton Rating Scale for Depression [HAM-D][39] score ≤ 5 and Young Mania Rating Scale [YMRS][40] score ≤ 5), and had to be on a stable treatment regimen for at least 1 month. Subjects with comorbid disorders that could be related to cognitive functioning (severe physical or neurologic illnesses, current or past alcohol or substance abuse or dependence, neurodegenerative disorders, mental retardation) were excluded. Healthy controls were recruited from the hospital's staff and from the patients' environment, and they had to be without a history of neurologic and/or psychiatric illness according to DSM-IV and had to have no first-degree relatives with a psychiatric disorder. The healthy controls were matched to patients on age, gender, and years of education.

Patients and controls gave written informed consent before entering the study. Ethical approval for the study was given by the Ethics Committee of the Ludwig-Maximilians-University in Munich. The study was conducted from 2002 through 2006.

Clinical Assessment

During a screening visit 1 month before entering the study, diagnosis and eligibility criteria were confirmed by using the Structured Clinical Interview for DSM-IV (German version[41]). Time in remission was assessed with the Life Chart Method[37] and psychopathology with the 21-item HAM-D, the YMRS, and the Positive and Negative Syndrome Scale[42] at screening and just before neuropsychological testing. Four weeks after the screening visit, the neuropsychological battery, the blood draw, and the clinical rating scales were assessed.

Cognitive Assessment

The neuropsychological assessment consisted of the Trail Making Test (TMT)[43] to determine information processing speed and cognitive flexibility, the German versions of the revised Wechsler Adult Intelligence Scale (WAIS-R) Information Subtest[44] to assess premorbid IQ, the Wechsler Adult Intelligence Scale III (WAIS-III) Letter-Number Sequencing Subtest (LNST)[45] to measure working memory, and the Repeatable Battery for the Assessment of Neuropsychological Status Form A (RBANS).[46]

The RBANS has 12 subtests that are used to calculate 5 index scores and a total score. Test indices are immediate memory (composed of the subtests List Learning and

Table 1. Demographic and Clinical Characteristics of Euthymic Bipolar Patients and Healthy Controls

Variable	Patients (N = 74)	Controls (N = 42)	Test	p Value
Age, mean ± SD (range), y	42.52 ± 12.23 (19–70)	43.02 ± 12.75 (21–65)	F = 0.04	.836
Female gender, %	50	52	χ^2 = 0.016	.805
Education, mean ± SD, y	11.64 ± 1.71	11.67 ± 1.65	F = 0.009	.923
HAM-D score, mean ± SD	1.36 ± 1.56	0.19 ± 0.5	F = 22.45	.000
YMRS score, mean ± SD	1.01 ± 1.45	0.10 ± 0.37	F = 16.24	.000
Diagnosis, N (%)				
Bipolar I	51 (69)			
Bipolar II	23 (31)			
Age at onset, mean ± SD (range), y	26.51 ± 10.1 (9–60)			
No. of episodes, mean ± SD (range)	11.6 ± 15.6 (2–99)			
Duration of illness, mean ± SD (range), y	16.7 ± 10.6 (1–43)			
Duration of euthymia, mean ± SD (range), mo	18.3 ± 36.8 (1–240)			

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Story Memory), visuospatial/constructional abilities (Figure Copy and Line Orientation), language (Picture Naming and Semantic Fluency), attention (Digit Span and Coding), and delayed memory (composed of List Recall, List Recognition, Story Recall, and Figure Recall). Each index score is an age-adjusted standard score with a mean of approximately 100 and a standard deviation of 15 based on a normative study group of 540 healthy U.S. subjects.

Assessment of Homocysteine Plasma Levels

To obtain homocysteine plasma levels, blood samples were collected in ethylene diamine tetracetic acid tubes, put on ice immediately, centrifuged within 15 minutes, and stored at –80°C. Total homocysteine plasma concentration was measured using high-performance liquid chromatography with fluorescence detection after derivatization according to a previously described method.[47,48] All blood samples were collected after the neuropsychological battery was administered; participants were not required to fast as this is no longer considered necessary for accurate determination of homocysteine plasma levels.[49]

Statistical Analyses

Patients and healthy controls were compared on clinical and demographic variables by using univariate analyses of variance (ANOVAs) and χ^2 tests as appropriate.

The raw scores of all neuropsychological tests were transformed into z scores on the basis of the data for the control group, which was matched by age, gender, and education. The z scores were then grouped by function (mean scores). Six cognitive domains were formed: information processing speed (Trail Making Test A [TMT-A] and RBANS subtest Coding), working memory (WAIS-III LNST and RBANS subtest Digit Span), verbal learning (RBANS subtests List Learning and Story Memory), visuospatial/constructional abilities (RBANS subtests Figure Copy and Line Orientation), delayed memory (composed of RBANS subtests List Recall, List Recognition, Story Recall, and Figure Recall), and executive functions (Trail Making Test B [TMT-B] and RBANS subtest Semantic Fluency). To standardize the results, the z scores of TMT-A and TMT-B were multiplied by –1.

A multivariate analysis of covariance (MANCOVA), with age as covariate, was conducted to compare neuropsychological performance between the 2 groups. When significant main effects were present, post hoc univariate tests with Bonferroni correction were performed. In a second step, HAM-D and YMRS scores were included as covariates into the model to control for subsyndromal symptoms. The magnitude of the differences between bipolar patients and healthy controls was calculated using Cohen's d.[50]

To test the impact of homocysteine levels on cognitive functioning in bipolar patients, Pearson's correlations and hierarchical regression analyses were carried out. In addition to the homocysteine level, clinical variables that were suggested to influence cognitive performance were introduced in the models using a stepwise method. Statistical significance was defined at a p value level ≤ .05. Analyses were done by using SPSS version 14.0 (SPSS, Inc.; Chicago, Ill.).

RESULTS

Participants

Seventy-five bipolar patients (52 bipolar I and 23 bipolar II patients) and 42 healthy controls were enrolled in the study. One bipolar I patient was excluded due to a depressive recurrence between screening and study visits. The demographic and clinical characteristics of both groups are shown in Table 1.

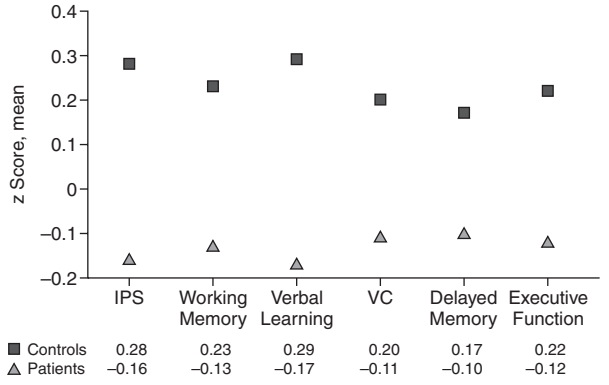
Five patients were not taking medication at the time of testing; all other patients were taking at least 1 mood stabilizer. Twenty-three patients were receiving monotherapy with a mood stabilizer, of whom 11 were receiving lithium (mean ± SD dosage: 1057.8 ± 341.5 mg/day), 7 were receiving lamotrigine (mean ± SD dosage: 262.5 ± 91.6 mg/day), 4 were receiving valproate (mean ± SD dosage:

Table 2. z Scores for Bipolar Patients and Healthy Controls

Cognitive Domain	Patients (N = 74), Mean ± SD	Controls (N = 42), Mean ± SD	F[a,b]	p Value	Effect Size, Cohen's d
Information processing speed	–0.16 ± 0.93	0.28 ± 0.81	9.20	.003	.50
Working memory	–0.13 ± 0.90	0.23 ± 0.85	4.75	.031	.41
Verbal learning	–0.17 ± 0.97	0.29 ± 0.55	9.37	.003	.58
Visuospatial/constructional abilities	–0.11 ± 0.86	0.20 ± 0.57	4.71	.032	.21
Delayed memory	–0.10 ± 0.83	0.17 ± 0.58	4.89	.029	.38
Executive function	–0.12 ± 0.92	0.22 ± 0.71	5.25	.024	.41

[a]Group comparisons done with multivariate analysis of covariance (age as covariate).
[b]df = 1,113.

Figure 1. z Scores for Neuropsychological Variables for Bipolar Patients and Healthy Controls



Abbreviations: IPS = information processing speed, VC = visuospatial/constructional abilities.

1262.5 ± 205.7 mg/day), and 1 was receiving oxcarbazepine (900 mg/day). Forty-six patients were taking more than 1 mood stabilizer. Eighteen patients were taking an atypical antipsychotic in addition to the mood stabilizer, and 4 patients were taking a typical antipsychotic (3 receiving perazine, 1 receiving haloperidol) in addition to the mood stabilizer. Nine patients were taking an antidepressant but none were taking benzodiazepines or anticholinergic medication at the time of testing.

Patients did not differ significantly from the healthy controls with respect to age (F = 0.043; df = 1,114; p = .836), gender (χ^2 = 0.016, p = .805), and years of education (F = 0.009; df = 1,114; p = .923; matching variables). When we looked only at the older individuals (> 50 years), both groups were still comparable in terms of gender (χ^2 = 0.47, p = .49). Differences were found in the HAM-D (F = 22.45; df = 1,114; p = .000) and YMRS scores (F = 16.24; df = 1,114; p = .000; Table 1).

The MANCOVA, with age as covariate, revealed a significant difference between bipolar patients and healthy controls on neuropsychological performance (Pillai-Spur: F = 3.32; df = 6,108; p = .038). Post hoc comparisons showed significant differences in all cognitive domains tested (Table 2 and Figure 1). However, after controlling for depressive and manic symptomatology, the differences between the groups in visuospatial/constructional abilities (F = 2.70; df = 1,111; p = .103) and working memory (F = 3.37; df = 1,111; p = .069) became insignificant, although overall cognitive performance (Pillai-Spur: F = 7.23; df = 6,106; p = .035) and post hoc comparisons still showed significant differences in information processing speed (F = 12.83; df = 1,111; p = .001), verbal learning (F = 5.98; df = 1,111; p = .016), delayed memory (F = 4.16; df = 1,111; p = .044), and executive function (F = 5.84; df = 1,111; p = .017). Neither subsyndromal depressive symptoms nor manic symptomatology had a significant effect on any cognitive domain in the MANCOVA ([HAM-D] Pillai-Spur: F = 0.99; df = 6,106; p = .430; [YMRS] Pillai-Spur: F = 0.67; df = 6,106; p = .673). The magnitude of the differences between the groups was in the small to moderate range (see Table 2).

Post hoc univariate ANOVAs of the raw scores of the tests showed that patients performed particularly worse than healthy controls on both subtests of the TMT and on the RBANS subtests that assessed verbal learning (List Learning, Story Memory), working memory (Digit Span), and information processing speed (Coding). No differences were found on visuospatial/constructional, delayed memory, or semantic fluency tests (Table 3).

Mean ± SD homocysteine levels were 10.2 ± 3.2 μM/L for the patients and 8.9 ± 2.8 μM/L for the control group. This difference was statistically significant (F = 4.51; df = 1,109; p = .036). Separated by gender, homocysteine levels were 9.2 ± 3.4 μM/L for women and 11.1 ± 2.8 μM/L for men in the bipolar group and 8.2 ± 2.2 μM/L and 9.6 ± 3.3 μM/L for the controls, respectively (Table 4). In the patient group, homocysteine levels significantly correlated with gender (r = .280, p = .019), number of psychotropic medications (r = .260, p = .029), treatment with antipsychotics (r = .249, p = .037), and body mass index (BMI) (r = .280, p = .047). They did not correlate with age, diagnosis, psychopathology, number of episodes, and the consumption of nicotine or caffeine (data not shown). Homocysteine levels also significantly correlated with verbal learning (r = –.343, p = .004) and executive function (r = –.291, p = .014). In addition, there was a trend in working memory (r = –.230, p = .052)

Table 3. Raw Scores of Bipolar Patients and Healthy Controls on Cognitive Tests

Cognitive Domain	Patients (N = 74), Mean ± SD	Controls (N = 42), Mean ± SD	F[a,b]	p Value
Premorbid IQ				
WAIS-R information	18.99 ± 3.45	20.12 ± 2.48	3.384	.068
Information processing speed				
TMT-A	31.09 ± 11.97	27.10 ± 9.82	4.880	.029
Coding	49.84 ± 11.56	55.62 ± 9.68	9.650	.002
Working memory				
WAIS-III LNST	12.68 ± 3.19	13.62 ± 2.75	2.760	.099
Digits Forward	11.68 ± 2.41	12.71 ± 2.40	4.967	.028
Verbal learning				
List Learning	31.66 ± 5.69	34.00 ± 3.72	7.191	.008
Story Memory	19.69 ± 3.86	21.31 ± 2.41	6.404	.013
Visuospatial/constructional abilities				
Figure Copy	18.35 ± 1.97	18.93 ± 1.28	3.238	.075
Line Orientation	18.42 ± 2.06	18.95 ± 1.43	2.338	.129
Delayed memory				
List Recall	7.28 ± 2.14	7.93 ± 2.03	3.526	.063
List Recognition	19.61 ± 0.96	19.64 ± 0.69	0.082	.775
Story Recall	9.89 ± 2.46	10.57 ± 1.56	2.926	.090
Figure Recall	15.39 ± 3.61	16.81 ± 2.23	6.322	.013
Executive function				
TMT-B	77.53 ± 40.34	61.12 ± 24.53	7.323	.008
Semantic Fluency (categorical)	22.68 ± 5.68	23.95 ± 4.98	1.593	.210

[a]Univariate analyses of variance with age as covariate.
[b]df = 1,113.
Abbreviations: LNST = Letter-Number Sequencing Subtest; TMT-A = Trail Making Test A, TMT-B = Trail Making Test B; WAIS-R = Wechsler Adult Intelligence Scale, revised; WAIS-III = Wechsler Adult Intelligence Scale III.

Table 4. Plasma Homocysteine Levels in Bipolar Patients and Healthy Controls

Variable	Patients (N = 70)	Controls (N = 41)	F[b]	p Value
Female gender, mean ± SD (range), μM/L	9.2 ± 3.4 (3.8–20.8)	8.2 ± 2.2 (5.0–12.3)	1.61	.209
Male gender, mean ± SD (range), μM/L	11.1 ± 2.8 (6.0–17.1)	9.6 ± 3.3 (6.4–20.1)	3.17	.080
Whole group, mean ± SD (range), μM/L[a]	10.2 ± 3.2 (3.8–20.8)	8.9 ± 2.8 (5.0–20.1)	4.51	.036

[a]Group comparisons done with analysis of variance.
[b]df = 1,109.

and delayed memory (r = –.232, p = .053), but no correlation between homocysteine level and information processing speed (r = –.140, p = .238) or visuospatial/constructional abilities (r = –.060, p = .619) could be detected. In the control group, homocysteine level correlated with age (r = .491, p = .001) but not with gender or any neuropsychological domain (data not shown).

To analyze whether the relationship of homocysteine levels and neuropsychological performance is independent from major confounders in the patient group, stepwise regression analyses were carried out with homocysteine level, age, gender, number of episodes, HAM-D and YMRS score, time of being euthymic, number of medications, current use of antipsychotics, and lifetime symptoms of psychosis as predictors.

Verbal learning was best predicted by homocysteine level (F = 9.01; df = 1,68; p = .004), with patients having higher homocysteine levels performing worse. Homocysteine levels predicted 11% of the variance. In a second model, homocysteine level and age strongly predicted verbal learning scores (F = 8.57; df = 1,67; p = .000). The delayed memory score was also predicted best by age and homocysteine level (F = 8.64; df = 1,67; p = .000), explaining 21% of the variance, whereas performance in executive function score was predicted by age at onset and homocysteine level (F = 8.52; df = 1,67; p = .001). No other variable entered the equation (Table 5).

Information processing speed was best predicted by age (F = 23.36; df = 1,68; p = .000). This sole predictor explained 25% of the variance. Older patients performed worse than younger ones. All other variables did not enter the equation. The working memory score was predicted only by the number of medications the patients were taking (F = 5.85; df = 1,68; p = .018), but only 8% of the variance was explained by this predictor. Finally, the visuospatial/constructional abilities were best predicted by age and lifetime symptoms of psychosis (F = 6.33; df = 1,68; p = .003). In a second step, BMI, smoking, and the different substance classes of medication were entered in the regression models, as these variables might modify homocysteine levels. However, no major changes occurred in the models applied.

Table 5. Regression Coefficients of the Regression Analyses in Bipolar Patients

Cognitive Domain	β	p Value	Estimated Difference
Verbal learning			
Homocysteine level	–.35	.002	–.171 to –.040
Age	–.29	.009	–.041 to –.006
Delayed memory			
Homocysteine level	–.24	.030	–.118 to –.006
Age	–.39	.001	–.042 to –.012
Executive function			
Homocysteine level	–.28	.011	–.141 to –.019
Age at onset	–.34	.002	–.050 to –.010
Information processing speed			
Age	–.51	.000	–.055 to –.023
Working memory			
No. of medications	–.28	.018	–.438 to –.042
Visuospatial/constructional abilities			
Age	–.36	.002	–.042 to –.009
Lifetime psychotic symptoms	–.25	.033	–.825 to –.036

DISCUSSION

Cognition

In our study, euthymic bipolar patients had small to moderate deficits in information processing speed, working memory, visuospatial/constructional abilities, verbal learning, delayed memory, and executive function compared to healthy controls. No significant differences were found in premorbid IQ. When depressive or manic subsyndromal symptoms were controlled, the differences between the 2 groups in visuospatial/constructional abilities and working memory became insignificant. These results are in line with other studies that showed differences between patients and healthy controls in tasks of executive function, information processing speed, and verbal learning[5,51–54] but showed less or no impairment in visuospatial/constructional abilities,[51,55–57] working memory,[58,59] or premorbid IQ.[60,61] The largest difference between the groups was found in verbal learning and information processing speed, which is in line with the meta-analysis conducted by Robinson and colleagues,[3] which found large effect sizes in these domains. Interestingly, when we examined the individual tests, we did not find any difference in categorical fluency, even though it showed the largest effect size in the meta-analysis.

Homocysteine and Cognition

Within the bipolar group, we could detect a significant association between homocysteine plasma levels and verbal learning, delayed memory, and executive function tasks. In the multiple regression analyses, we found that homocysteine levels predicted a worse performance in those domains, independent of age, gender, subsyndromal symptoms, number and type of medication, obesity, smoking, or other demographic and clinical variables. This finding is in line with studies of healthy individuals,[11,17,19] in which performance in memory and executive function tasks were also associated with homocysteine plasma levels. Our results point also in the same direction as findings of an article just published: Osher et al.[62] found an association of elevated homocysteine levels and both the perseverative errors and the completed categories of the Wisconsin Card Sorting Test, a measure of executive function. But while those authors could find a relationship with only executive function tasks, we were able to detect that and also detect an association of homocysteine with verbal learning and delayed memory.

Most likely, cognitive impairment in bipolar patients is due to multiple factors. According to our results, homocysteine might be 1 contributing factor. Correlations between homocysteine and cognition have also been found in other psychiatric disorders as well as in healthy elderly people. Thus, homocysteine might not be specific for bipolar disorder. Therefore, it might be suggested that the association between homocysteine and cognitive impairment in bipolar patients primarily resembles a general sensitivity against neurotoxic agents like homocysteine, as it has been shown with arecoline.[63]

Similar to schizophrenia,[64] bipolar disorder seems to be associated with dysfunctions in the glutamatergic system[65,66] and apoptosis.[67,68] Furthermore, oxidative stress may play an important role, at least in mania.[67] Homocysteine interferes with these mechanisms, and, while it may not be the sole trigger, a slight homocysteine level elevation could have negative consequences on the homeostasis of these complex mechanisms and thus contribute to cognitive impairment. Additionally, homocysteine did not correlate with age in bipolar patients, which suggests that bipolar patients might have elevated homocysteine levels at a much younger age. Our finding suggests that homocysteine plasma levels may contribute to impairments in verbal learning, delayed memory, and executive function in bipolar disorder. It might be partly explained by a common final pathway that starts earlier in bipolar patients compared to healthy controls due to a higher sensitivity and higher homocysteine levels at younger ages in bipolar patients. However, distinct pathomechanisms remain speculative and have to be answered by further studies.

Homocysteine levels may be influenced by obesity, smoking, alcohol abuse, medication, and poor nutrition. In our sample, homocysteine levels correlated with BMI, gender, and number of psychotropic medications but not with smoking. Regardless of its origin, homocysteine seems to be an independent predictor for delayed memory, verbal learning, and executive functioning, at least in patients with bipolar disorder, and might therefore be an interesting biomarker for existing or developing cognitive impairment.

While studies in healthy elderly people could also show a correlation between homocysteine levels and information processing speed and visuospatial/

constructional abilities, we did not find such an association, neither in bipolar patients nor in healthy controls. Instead, the numbers of psychotropic medication that patients were taking had an impact on working memory. Similarly, the presence of psychotic symptoms negatively affected visuospatial/constructional abilities. While studies conducted by Frangou and colleagues[54,69] reported that antipsychotic medication has a negative impact on memory performance, general IQ, and executive function, our results could not confirm these findings. In contrast to that group, antipsychotic medication did not turn out as an independent predictor for memory or executive function. However, the number of psychotropic drugs had a major impact on information processing speed. Our results point in the same direction as those by Martinez-Aran et al.[52] and Glahn and colleagues,[70] who could show that the lifetime occurrence of psychotic symptoms predicted performance on some cognitive domains, such as working memory.

Limitations

Our study has several limitations. For example, all patients except 5 were taking medication at the time of neuropsychological testing. Combined treatments and different dosages are common in bipolar patients as in our study population. Ideally, drug-free euthymic patients should be examined. However, from an ethical as well as clinical point of view, this is hard to justify.

Homocysteine levels may be influenced by medication, poor nutrition, smoking, obesity, or alcohol use. Even though patients with current or past alcohol or substance abuse or dependence were excluded, we did not obtain detailed information on participants' alcohol use at the time of study entry. We also did not systematically collect information on folate and B_{12} serum levels in all of our patients; therefore, we do not know whether the elevated homocysteine levels in our patients are due to folate and B_{12} levels below the reference range. However, in the 20% of patients in which this information was available, levels were found to be within the normal range.

Finally, the results of the study are limited by the cross-sectional design. Longitudinal studies of bipolar patients are needed to clarify the stability of the observed association between elevated homocysteine level and poor performance in verbal learning, delayed memory, and executive functions.

CONCLUSION

To our knowledge, this is the first study to show an association between verbal learning, delayed memory, and executive functions and homocysteine plasma levels in euthymic bipolar patients. This relationship is clinically significant since lowering homocysteine levels has been associated with positive effects on several cognitive domains in healthy elderly subjects.[20] Further studies, including intervention studies with folic acid, B_{12}, and B_6, are therefore urgently needed to further explore the relationship between homocysteine levels and cognitive functioning in bipolar disorder.

Drug names: haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), oxcarbazepine (Trileptal and others), perazine (Compro, Stelazine, and others).

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