

Original Article

Association of cognitive deficits with elevated homocysteine levels in euthymic bipolar patients and its impact on psychosocial functioning: preliminary results

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Objectives: Elevated homocysteine (Hcy) levels have been demonstrated to have a negative impact on cognitive functioning in healthy elderly people. Further studies suggest that they are an independent risk factor for dementia, in particular for Alzheimer's disease. Bipolar disorder is also associated with cognitive impairment. However, the pathophysiological mechanisms of these deficits have not been elucidated yet. This study examines the role of Hcy on cognition and its impact on psychosocial functioning in euthymic bipolar patients.

Methods: A total of 55 euthymic bipolar patients and 17 healthy controls were enrolled in the study. Neuropsychological assessments consisted of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Trail Making Test (TMT), the Weschler Adult Intelligence Scale, 3rd edition (WAIS-III) subtest Letter–Number Sequencing Test (LNST) and the HAWIE-R (German version of the WAIS-R) subtest Information. Psychosocial functioning was assessed using the Social Adjustment Scale (SAS). To obtain plasma levels of Hcy, blood samples were collected in EDTA tubes, immediately put on ice, centrifuged within 15 min and stored at –80°C. Total Hcy concentration was measured using high-performance liquid chromatography.

Results: In the neuropsychological tests, patients differed significantly from healthy controls on the TMT B and the RBANS composite indices Language, Attention and Total Score. No differences were found on the HAWIE-R subtest Information, the TMT A, LNST or the RBANS composite indices Immediate Memory, Visuospatial/Constructional Abilities and Delayed Memory. Mean Hcy levels were $9.8 \pm 3.2 \mu\text{m/L}$ in the patient group and $7.8 \pm 2.1 \mu\text{m/L}$ in the control group, respectively ($p = 0.012$). In the patient group Hcy levels significantly correlated with gender, diagnosis and RBANS index scores for Immediate Memory, Language, Attention and Total Score. Linear regression analyses revealed a significant and independent association of Hcy levels with Immediate Memory and TMT B scores in the patient group. Homocysteine levels did not correlate with any measure in the control group. Spearman's correlations indicated that psychosocial functioning in bipolar patients is not associated with clinical variables apart from

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time in remission. However, it correlated significantly with working memory measures (LNST). No relationship could be determined between psychosocial functioning and Hcy plasma levels.

Conclusions: Elevated Hcy levels seem to be associated with cognitive impairment in euthymic bipolar patients, but not with psychosocial functioning. More studies are needed to clarify the role of Hcy in cognition in bipolar disorder.

There is growing evidence that patients with bipolar disorder (BD) suffer from cognitive impairment during euthymia (1–3). In most studies, stable bipolar patients perform worse than healthy controls on neuropsychological tests of attention (4–7), verbal (1, 3, 8, 9) and non-verbal memory (10, 11) and executive function (12–14). Despite methodological differences between these studies, there is a broad consensus that euthymic bipolar patients have cognitive deficits in these specific domains compared to healthy controls (1, 2). By contrast, there does not seem to be any difference with regard to general intellectual functioning or overall IQ (6, 10, 11, 15). Recent reports have emphasized the impact of cognitive dysfunction on psychosocial functioning in bipolar patients (3, 13, 16, 17). In addition, similar to what we know from schizophrenia, psychosocial functioning seems to be more strongly associated with cognitive impairment than most other clinical variables (18).

However, the neuro-anatomical background of these deficits is still largely unknown. Prefrontal as well as subcortical abnormalities and possible disruptions of cortical–subcortical circuits have been discussed (19, 20). This is in line with findings from structural as well as functional neuroimaging studies (2, 21). For example, some studies found higher rates of hyperintensities in the deep white matter, in the periventricular white matter and in the subcortical gray matter in the frontal lobe of bipolar patients (reviews in 2, 21), compared with healthy controls. In addition, these hyperintensities occur more frequently in bipolar patients than in schizophrenic or unipolar patients and seem to be correlated with cognitive impairment (22, 23) in many but not all studies (24). Interestingly, white matter hyperintensities do not seem to be associated with age or vascular risk factors in bipolar patients (2).

The last few years have witnessed growing evidence that an elevated plasma homocysteine (Hcy) level is a risk factor for cognitive impairment, dementia and, particularly, Alzheimer's disease, and is associated with white matter lesions and silent brain infarcts in healthy elderly people (25–33).

Homocysteine, a sulfur-containing amino acid that is part of the methionine metabolism, might affect cognitive function in several ways. For example, it might represent a marker for an insufficient supply of the B vitamins due to nutritional deficiency and/or reduced glomerular filtration rate (34). In addition, high Hcy levels might contribute to cognitive impairment by causing silent brain infarcts. Furthermore, oxidized forms of Hcy, such as homocysteic acid, are potent neurotoxic agents leading to apoptosis and leukaraiosis (29, 35). It is also likely that disturbances in methylation pathways, including methylation of DNA, neurotransmitters and phospholipids, will have negative consequences for the function of cerebral tissue (36). For example, Kruman et al. (37) demonstrated that Hcy elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity.

Furthermore, elevated Hcy levels have been reported in other psychiatric disorders, such as schizophrenia (38–40) and unipolar depression (41–43), although not in all studies (44). One study also found greater functional deterioration in bipolar subjects with elevated Hcy levels compared to those with plasma levels in the normal range (45).

The present study aimed to analyze the association between neuropsychological measures and plasma levels of Hcy in bipolar patients. We hypothesized that patients as well as healthy controls with elevated Hcy levels would perform worse on neuropsychological tests assessing memory and psychomotor speed compared to subjects with Hcy levels in the normal range. In addition, we hypothesized that Hcy levels are associated with age and gender in all subjects. Finally, psychosocial functioning was hypothesized to be associated with cognitive impairment in the patient group.

This paper presents the preliminary results of an ongoing study.

Methods

Subjects

Patients participating in the present study were enrolled in the Stanley Foundation Bipolar Network at the Bipolar Outpatient Clinic of the

Department of Psychiatry, University of Munich. Patients were diagnosed with BD according to DSM-IV criteria and had to have been euthymic for at least 1 month on a stable treatment regimen [Hamilton Depression Scale (HAM-D) score ≤ 5 and Young Mania Rating Scale (YMRS) score ≤ 5]. Subjects with comorbid disorders known to affect cognitive functioning (severe physical or neurological illnesses, present alcohol or substance abuse or dependence, neurodegenerative disorders, mental retardation) were excluded from the study. Healthy controls had to be free of a personal history of neurological or psychiatric illness [confirmed with the Structured Clinical Interview for DSM-IV, SCID-DSM-IV, German version (46)] and had to have no first-degree relative with a psychiatric disorder. Healthy controls were matched for age, gender and education.

Patients and controls gave written informed consent before entering the study. Ethical approval for the study was granted by the Institutional Review Board (IRB) of the University of Munich.

Clinical and psychosocial assessments

All subjects underwent the SCID DSM-IV (46) to confirm diagnosis. The German versions of the HAM-D (21 items) (47), the YMRS (48) and the Positive and Negative Syndrome Scale (PANSS) (49) were used to assess psychopathology at the time of neurocognitive testing.

Psychosocial functioning was rated with the Social Adjustment Scale (SAS) by Weissman and Bothwell (50, 51). The scale includes questions on paid work, work in the household, work as a student, social and leisure activities, relationships with family members and friends. Scores are summarized into four social and occupational areas (work, household, social life and overall functioning) and range from excellent (rated as 1) to extremely poor (rated as 7).

Neuropsychological assessments

Neuropsychological assessments consisted of the Repeatable Battery for the Assessment of Neuropsychological Status Form A (RBANS) (52), the Trail Making Test (TMT) (53), the Wechsler Adult Intelligence Scale-III (WAIS-III) subtest Letter-Number Sequencing Test (LNST) (54) and the HAWIE-R (German version of the WAIS-R) subtest Information.

The RBANS consists of 12 subtests that are used to calculate five index scores and a total score. Test indices are Immediate Memory (comprised of the subtests List Learning and Story Memory),

Visuospatial/Constructional Abilities (Figure Copy and Line Orientation), Language (Picture Naming and Semantic Fluency), Attention (Digit Span and Coding), and Delayed Memory (comprised 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 American subjects. No normative data for German subjects exist so far. The index scores are combined to calculate the Total Score, which represents a measure of overall cognitive functioning.

To determine psychomotor speed and set, shifting TMTs A and B were used. Premorbid IQ was estimated with the HAWIE-R subtest Information and working memory was assessed with the WAIS-III subtest LNST.

Laboratory assessments

To obtain plasma Hcy levels, blood samples were collected in EDTA (ethylenediaminetetraacetic acid) tubes, immediately put on ice, centrifuged within 15 min and stored at -80°C . Total Hcy concentration was measured using high-performance liquid chromatography (HPLC) with fluorescence detection after derivatization according to a previously described method (55, 56). All blood samples were collected from non-fasting individuals after the neuropsychological battery, because fasting is no longer considered a requirement for accurate determination of Hcy levels (57).

Statistical analyses

Differences between patients and healthy controls were tested using Wilcoxon's test and Fisher's exact test. To test the influence of Hcy on cognitive functioning, multiple regression analyses were carried out. As well as Hcy levels, age, gender, number of previous episodes, HAM-D score and number of psychotropic medications were included as independent variables in order to account for major confounders. Spearman's correlations were used to analyze relationships between cognitive functioning and clinical variables as well as psychosocial functioning. Statistical significance was defined as $p \leq 0.05$. Analyses were performed using SAS Version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 55 bipolar patients (29 females, 26 males) and 17 healthy controls (9 females, 8 males) were enrolled in the study. The patient group consisted of

39 bipolar I patients (71%), 13 patients with BD II (24%) and three patients with a schizoaffective disorder, bipolar type (5%). Patients were treated at the discretion of the psychiatrist in charge. Five patients were off medication at the time of testing; all other patients were using ≥ 1 mood stabilizer. Eleven patients were treated only with lithium (mean dosage: 1057.78 ± 341.54 mg/day), eight with lamotrigine (mean dosage: 262.5 ± 91.6 mg/day), four with valproate (mean dosage: 1262.5 ± 205.65 mg/day) and one with oxcarbazepine (900 mg/day). Ten patients were using ≥ 1 mood stabilizer. A total of 21 patients took an antipsychotic (18 with atypical antipsychotics) in addition to the mood stabilizer. Nine patients took an antidepressant. None were taking benzodiazepines.

Patients did not differ significantly from healthy controls concerning, age, gender and education. Differences were found concerning HAM-D scores, but not in YMRS scores. Table 1 shows the characteristics of the two groups.

In the neuropsychological tests, both groups differed significantly on TMT B scores and on the composite RBANS indices Language, Attention and Total Score. No differences with healthy controls were found on the HAWIE-R subtest Information, the TMT A, LNST or on the RBANS composite indices Immediate Memory, Visuospatial/Constructional Abilities and Delayed Memory (Table 2). The results of the neuropsychological tests did not correlate with manic or depressive symptoms, number of episodes or diagnosis (data not shown).

Mean Hcy levels were 9.8 ± 3.2 $\mu\text{m/L}$ in the patient group and 7.8 ± 2.1 $\mu\text{m/L}$ in the control group. This difference was statistically significant ($p = 0.012$). The data, separated for gender, are shown in Table 3. In the bipolar sample, Hcy levels correlated significantly with gender, diagnosis and the RBANS composite measures Immediate Mem-

ory, Language, Attention and Total Score. They did not correlate with HAM-D or YMRS scores or time in remission. In the control group the Hcy levels did not correlate with any measure (data not shown). Multiple regression analyses were carried out to determine whether the association of Hcy levels with the neuropsychological test results was independent of gender, age, number of previous episodes, HAM-D score or medication.

TMT A, TMT B and the RBANS index scores Immediate Memory, Language, Attention and Total Score were significantly predicted from a linear regression that included Hcy levels, gender, age, number of previous episodes, HAM-D score and the number of psychotropic medications as independent variables (Table 4). A significant and independent association of Hcy plasma levels with Immediate Memory and TMT B scores was revealed. TMT A score was predicted by age and Attention by number of psychotropic medications. The scores of the HAWIE-R subtest Information, LNST, Delayed Memory and Visuospatial/Constructional Abilities indices were not predicted in this linear regression model.

Psychosocial functioning was assessed with the Social Adjustment Scale (SAS). While all healthy controls had good to very good overall psychosocial functioning (rated as 2–3), only 61% of the patients displayed good to very good overall functioning. A total of 25% of patients functioned moderately and 14% functioned poorly or very poorly (rated as 5–6). None of the patients had extremely poor functioning (rated as 7).

Spearman's correlations indicated that psychosocial functioning (overall SAS score) in bipolar patients was not associated with clinical measures apart from time in remission (Table 5). However, overall psychosocial functioning was significantly correlated with age and the neuropsychological measures of working memory (LNST) and cogni-

Table 1. Demographic and clinical characteristics of patients and controls

Variables	Bipolar group (n = 55)	Control group (n = 17)	p-value
Gender ^a	29 female (52.7%)	9 female (52.9%)	1.0
Age ^b	42.3 ± 12.8	37.7 ± 8.9	0.257
Education ^b	11.7 ± 1.7	11.82 ± 1.6	0.447
HAM-D ^b	1.11 ± 1.39 (range 0–5)	0 ± 0	0.000 ^c
YMRS ^b	0.52 ± 1.4 (range 0–5)	0.18 ± 0.84 (range 0–2)	0.063
Age of onset	26.51 ± 10.1		
Episodes	11.6 ± 15.6		
Duration of illness (years)	16.7 ± 10.6		
Time in remission (months)	18.3 ± 36.8 (range 1–240)		

HAM-D = Hamilton Depression Rating Scale; YMRS = Young Mania Rating Scale.

^aGroup comparisons performed with Fisher's exact test.

^bGroup comparisons performed with Wilcoxon test.

^c $p < 0.05$.

Table 2. Performance on neuropsychological tests by bipolar patients and healthy controls

Variables	Bipolar group (n = 55)	Control group (n = 17)	p-value ^a
HAWIE-R subtest Information	18.6 ± 3.3	20.2 ± 2.2	0.052
TMT A	32.18 ± 12.64	26.6 ± 11.85	0.113
TMT B	81.16 ± 43.84	60.53 ± 30.77	0.031 ^b
LNST	12.51 ± 3.16	13.53 ± 3.17	0.409
RBANS index scores			
Immediate memory	108.53 ± 20.1	116.65 ± 11.6	0.122
Visuospatial/Constructional	102.35 ± 15.3	101.59 ± 14.8	0.785
Language	101.15 ± 11.5	108.53 ± 10.7	0.011 ^b
Attention	97.67 ± 17.6	106.06 ± 12.7	0.034 ^b
Delayed Memory	100.18 ± 13.7	104.41 ± 8.3	0.227
Total RBANS score	103.07 ± 16.7	110.35 ± 12.3	0.047 ^b

HAWIE-R = German version of the WAIS-R; TMT = Trail Making Test; LNST = Letter-Number Sequencing Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

^aGroup comparisons performed with Wilcoxon test.

^bp < 0.05.

Table 3. Plasma homocysteine levels (in µm/L) in patients and controls

	Female	Male	Whole group
Bipolar group	8.5 ± 2.9	11.2 ± 3.1	9.8 ± 3.2
Controls	7.7 ± 2.3	7.9 ± 1.9	7.8 ± 2.1
p-value	0.736	0.003 ^a	0.012 ^a

Group comparisons performed with Wilcoxon test.

^ap < 0.05.

tive flexibility (TMT B; see Table 5). When age was factored out, the association between LNST and SAS scores remained significant ($r = -0.31$, $p < 0.028$), whereas TMT B and SAS scores no longer correlated significantly ($r = 0.248$, $p = 0.082$), suggesting that the association between cognitive flexibility and psychosocial functioning might be mediated by age.

Table 4. Regression coefficients ± standard error in regression analyses

	Age	Episodes	Gender	HAM-D score	Hcy levels (µm/L)	Number of meds	F (6, 32)	p-value
TMT A	0.692 ± 0.158 ^b	-0.224 ± 0.155	0.512 ± 4.992	-0.591 ± 1.69	0.448 ± 0.764	1.105 ± 2.099	3.61	0.008 ^b
TMT B	2.198 ± 0.540 ^b	-0.468 ± 0.527	-6.486 ± 17.022	-5.461 ± 5.764	5.679 ± 2.607 ^a	1.289 ± 7.157	3.97	0.004 ^b
HAWIE-R	-0.044 ± 0.045	0.016 ± 0.044	2.865 ± 1.429	-0.050 ± 0.484	-0.595 ± 0.219 ^b	0.354 ± 0.601	1.66	0.163
LNST	-0.086 ± 0.044	0.052 ± 0.043	1.838 ± 1.386	-0.343 ± 0.469	-0.517 ± 0.212 ^a	-0.187 ± 0.583	1.94	0.104
Repeatable Battery for the Assessment of Neuropsychological Status								
Immediate Memory	0.026 ± 0.258	0.299 ± 0.252	-3.130 ± 8.151	-2.518 ± 2.760	-3.282 ± 1.248 ^a	1.903 ± 3.427	2.87	0.024 ^a
Visuospatial/Constructional	-0.027 ± 0.191	-0.109 ± 0.187	-2.852 ± 6.039	2.755 ± 2.045	0.320 ± 0.925	-6.728 ± 2.539 ^a	1.63	0.170
Language	-0.101 ± 0.136	0.303 ± 0.133 ^a	-3.461 ± 4.297	-1.350 ± 1.455	-1.051 ± 0.658	-0.673 ± 1.807	2.87	0.024 ^a
Attention	0.128 ± 0.220	0.175 ± 0.215	-3.349 ± 6.928	0.244 ± 2.346	-0.954 ± 1.061	-7.104 ± 2.913 ^a	2.89	0.023 ^a
Delayed Memory	-0.121 ± 0.148	0.117 ± 0.145	-11.045 ± 4.683 ^a	2.473 ± 1.586	-0.306 ± 0.717	-0.319 ± 1.969	2.37	0.053
Total Score	0.006 ± 0.189	0.278 ± 0.185	-7.140 ± 5.977	0.538 ± 2.024	-1.383 ± 0.915	-3.917 ± 2.513	3.77	0.006 ^b

HAM-D = Hamilton Depression Rating Scale; Hcy = homocysteine levels; TMT = Trail Making Test; HAWIE-R = German version of the WAIS-R; LNST = Letter-Number Sequencing Test.

^ap < 0.05; ^bp < 0.01.

Discussion

The results of this study suggest that euthymic bipolar patients have deficits in cognitive flexibility, attention and language tasks compared to healthy controls. No differences were found concerning the HAWIE-R subtest Information (as a measure for pre-morbid IQ), psychomotor speed, and measures of Working Memory (LNST), Immediate Memory, Visuospatial/Constructional Abilities and Delayed Memory. This is in line with other studies that have shown cognitive impairment in tasks of executive function, attention and verbal skills (1, 3, 4, 6, 18). Interestingly we could not find any differences in immediate or delayed verbal and non-verbal memory tasks between patients and controls, although deficits in these domains seem to be among the most robust findings in the literature (1, 2). The

Table 5. Spearman's correlations of psychosocial functioning (Social Adjustment Scale, overall score) with demographic, clinical and neuropsychological variables by (n = 51)

	Spearman's rho	p-value
Demographic variables		
Age	0.385	0.005 ^a
Gender	0.035	0.808
Diagnosis	-0.082	0.566
Education	-0.179	0.208
Number of episodes	0.292	0.068
Duration of illness	0.262	0.077
Time in remission	-0.323	0.037 ^b
Age of onset	0.143	0.342
Homocysteine plasma level	-0.094	0.528
Neuropsychological measures		
HAWIE-R subtest information	-0.110	0.441
TMT A	0.166	0.243
TMT B	0.319	0.022 ^b
LNST	-0.336	0.016 ^b
RBANS index scores		
Immediate Memory	-0.113	0.430
Visuospatial/Constructional	-0.179	0.208
Language	-0.063	0.659
Attention	-0.136	0.343
Delayed Memory	-0.211	0.136
Total RBANS score	-0.166	0.245

HAWIE-R = German version of the WAIS-R; TMT = Trail Making Test; LNST = Letter-Number Sequencing Test; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

^ap < 0.01; ^bp < 0.05.

small size of the control group and subsequent lack of statistical power might account for this finding. Using the same neuropsychological battery on a larger study population, Dickerson et al. (58) were able to detect significant and clinically relevant differences between bipolar patients and healthy controls in almost all cognitive domains.

Another explanation for the discrepancy between the results from our study and those from the study by Dickerson et al. (58) may concern the fact that our patients were very stable for quite a long time and had low scores on all psychopathological rating scales. Most of the patients we tested had been in remission for > 1 year and had HAM-D and YMRS scores < 5, which implies that psychopathology might not have confounded the neuropsychological results. This is in line with our finding that neither HAM-D nor YMRS scores correlated with any of the neuropsychological measures or predicted any neuropsychological measure within the bipolar group.

We did find a significant difference in Hcy plasma levels between euthymic bipolar patients and healthy controls, thus confirming the results of Levine et al. (59) and Osher et al. (45). However, unlike their studies, the difference between our two

groups in Hcy levels was quite small. This may be due to differences in the methodology of sampling and analyzing blood, or different lifestyle habits or treatment schemes (like folate fortification) which were not controlled for in these studies.

Furthermore, medication (such as antiepileptic drugs) (60) as well as depression (41) might be associated with increased Hcy levels. This may be another reason for the difference between healthy controls and bipolar patients. However, in our study, neither HAM-D or YMRS scores nor medication correlated with Hcy levels in the patient group. In addition, none of our patients on valproate (n = 4) or patients in short-term remission from an acute episode (n = 2) had elevated Hcy levels.

Within the bipolar group we were able to detect an association between elevated Hcy levels and verbal memory tasks and cognitive flexibility. In the multiple regression analyses elevated Hcy levels predicted worse performance on immediate memory tasks, as well as on TMT B, independent of age, gender or medication. This is in line with studies in healthy elderly people, which also demonstrated a clear association between memory tasks, cognitive flexibility, psychomotor speed and high Hcy plasma levels (29). Although we were unable to detect significant differences on memory tasks between the groups in our study, Hcy levels above the normal range may represent a missing link in the pathophysiology of memory impairment in BD. Whether Hcy itself or any of its metabolites damages brain tissue in patients with BD and thus leads to cognitive impairment, or whether another underlying mechanism is responsible for both elevated Hcy levels and cognitive impairment in bipolar patients still needs to be elucidated. Larger studies and clinical trials that aim to treat cognitive impairment and elevated Hcy levels need to be conducted to clarify the role of Hcy in cognitive impairment in BD.

In contrast with the study by Osher et al. (45), which showed a significant association between Hcy and functional deterioration, our study was unable to confirm these results. One reason might be the different methodology used. However, working memory showed an association with psychosocial functioning, thus confirming the results of Martinez-Aran et al. (3).

Limitations

One clear limitation of this study is the small sample size of the control group. This led to low statistical power, which made it impossible to include clinical variables, which may confound the results of neuropsychological tasks.

All patients except five were on medication at the time of neuropsychological testing. Combined treatments and different dosages are common in bipolar patients, as in our study population. To eliminate the effects of drugs on cognitive functioning, drug-free euthymic patients should be examined, but such patients are rare.

In order to establish a causal association between Hcy plasma levels and cognitive functioning in bipolar patients, possible other confounders that might modify Hcy levels have to be considered. While we have incorporated medication, gender and age as potential predictors, poor nutrition, genetic factors, smoking, overweight or alcohol use were not controlled for. However, patients with alcohol or substance abuse or dependence were excluded. Therefore, larger studies are clearly needed to control for these variables.

Finally, the results of this study are limited by its cross-sectional design. Longitudinal studies of first episode bipolar patients or high-risk populations are needed to clarify whether cognitive deficits in bipolar patients are related to the illness or to other variables and to establish whether there is a causal relationship between Hcy levels and memory impairment.

Conclusions

To our knowledge this is the first prospective study to show an association between neuropsychological measures and elevated Hcy levels in euthymic bipolar patients. Further studies are needed to analyze whether there is a robust causal relationship between high Hcy levels and memory impairment and cognitive flexibility. This is of special importance as Hcy levels can be normalized by supplementation with folic acid and vitamins B6 and B12. As the pathophysiology of cognitive deficits in BD is still largely unknown, further studies are needed to elucidate the relationships between cognitive deficits, Hcy levels and brain abnormalities, such as white matter lesions.

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