

Homocysteine and Cognitive Function in Geriatric Depression

P. Alexopoulos^{a, b} S. Topalidis^a G. Irmisch^a K. Prehn^a S.U. Jung^a K. Poppe^a
H. Sebb^a R. Perneczky^b A. Kurz^b S. Bleich^c S.C. Herpertz^a

Departments of Psychiatry and Psychotherapy, ^aUniversity of Rostock, Rostock, and ^bTechnische Universität München, Munich, and ^cDepartment of Psychiatry, Social Psychiatry and Psychotherapy, Medical University of Hannover, Hannover, Germany

Key Words

Serum homocysteine · Information processing · Processing speed · Geriatric depression

Abstract

Background/Objectives: Cognitive dysfunction is a common aspect of the spectrum of symptoms of geriatric depression. High homocysteine levels have been linked to cognitive decline in neuropsychiatric disorders. The present study investigated possible associations between cognitive impairment observed in geriatric depression and homocysteine levels. **Methods:** The performance of 25 mentally healthy individuals and 40 patients with geriatric depression in terms of language processing, processing speed, concentration and attention was assessed with the Stroop Test and the d2 Test of Attention. Serum homocysteine was determined with an enzyme immunoassay. **Results:** The performance of depressed patients was significantly worse in language processing ($p = 0.001$) and processing speed ($p < 0.0001$). Depressed patients with high levels of homocysteine performed better than patients with homocysteine concentrations $\leq 11.7 \mu\text{mol/l}$ in both cognitive domains ($p = 0.006$ and 0.009 , respectively). Moreover, homocysteine level was positively associated with language processing ($p = 0.002$) and processing speed ($p = 0.002$). **Conclusions:** These findings indicate that under the special circumstances of ge-

riatic depression (perturbation of glutamatergic transmission and glutamate metabolism), homocysteine is positively associated with the performance in language processing and processing speed.

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Introduction

The scientific and clinical interest surrounding geriatric depression has progressively increased. The prevalence of depression ranges from 8.8 to 18.3% in people aged 60 years or older [1] and as a result of population ageing, it has become a major public health concern. In addition to depressed mood, the spectrum of symptoms of geriatric depression often includes loss of interest and pleasure, marked loss of appetite, or marked psychomotor retardation or agitation, and deficits in cognitive functions not developing on the ground of neurodegeneration [2, 3]. Elderly individuals with depression particularly exhibit disturbances in information processing, executive functioning, visuospatial ability and psychomotor speed [4]. Cognitive deficits developing on the ground of geriatric depression are of great clinical significance, since they are associated with a poor or delayed antidepressant response as well as with early relapse and recurrence of depressive symptoms [5]. Based on findings

from structural neuroimaging, diffusion tensor imaging, neuropsychological assessment and electrophysiological studies, a current model of the underlying brain dysfunction in geriatric depression posits that the frontostriatal cognitive circuits are affected [6].

Homocysteine, a nonessential sulfur-containing amino acid, is considered to make a direct or additional contribution to cognitive decline. The theory that elevated plasma homocysteine levels constitute a risk factor for cognitive impairment in a plethora of neuropsychiatric conditions arises from observations of several studies, revealing associations between cognition deficits and hyperhomocysteinemia, which possibly affects long-term potentiation [7]. Increased homocysteine levels are linked to Alzheimer's disease, as first reported by Regland et al. [8] and also observed in histologically confirmed cases by Clarke et al. [9]. Recently, elevated plasma homocysteine levels have been shown to increase the risk of Alzheimer's disease [10]. Furthermore, elevated homocysteine concentrations have been associated with adverse function in memory and psychomotor speed in nondemented elderly individuals, whose performance was measured with the Stroop Test, the Letter-Digit Substitution Task, a Paper-and-Pencil Memory Scanning Task and a 15-word verbal learning test based on Rey's Recall of Words [11]. In elderly nondemented individuals, homocysteine levels have also been shown to correlate negatively with scores in Raven's Progressive Matrices and in the Digit Symbol and Block Design subtests of the revised Wechsler Adult Intelligence Scale [12]. Moreover, in patients undergoing alcohol withdrawal, increased homocysteine concentrations have been associated with short-term cognition deficits detected with the c.I.-Test [13]. Concerning depression, Bell et al. [14], to our knowledge the only research group that has investigated possible associations between homocysteine and cognitive screening test scores in patients with geriatric depression, found that in elderly patients with depression and without concomitant vascular diseases, higher plasma homocysteine correlated with poorer cognitive performance. The neuropsychological examination was, however, limited to the Mini-Mental State Examination (MMSE), and patients with dementia were not excluded from the geriatric depression sample. Nonetheless, not all studies consistently report a negative correlation between homocysteine levels and cognitive function: in females with eating disorders moderately elevated plasma homocysteine levels have been related to normal short- and long-term verbal memory performance, which was assessed with the Logical Memory subscale of the Wechsler Memory Screen

Revised, whereas normal plasma homocysteine concentrations seem to be associated with poorer memory performance [15].

The objective of the present study was to investigate whether homocysteine is associated with the performance of depressed patients in cognitive domains that are particularly affected in geriatric depression such as language processing, processing speed, concentration and attention.

Methods

Study Sample

Forty patients older than 60 years with current unipolar depression were enrolled in the study. Age at onset of the first depressive episode was over 60, as determined from information obtained in the interview. All patients were living independently and had sought treatment at the Department of Psychiatry and Psychotherapy of the University Hospital of Rostock, Germany. Twenty-five elderly control subjects with no psychiatric history of mood or psychotic disorders who showed no signs of current psychiatric illness were recruited by advertisement.

The diagnostic procedure included history taken from the patient according to the Structured Clinical Interview for Axis I DSM-IV (American Psychiatric Association 1994) Disorders and from an informant; medical, neurological, and psychiatric examination; laboratory screening, brain imaging (computed tomography or magnetic resonance imaging), global neurocognitive evaluation using the MMSE [16], DemTect [17] and the dementia section of the Test for the Early Detection of Dementia with Differentiation from Depression (TE4D) [18] in order to rule out subjects with very mild dementia; the Motor Agitation and Retardation Scale [19]; rating of the severity of depressive symptoms using the 21-item Hamilton Depression Scale [20] and the depression section of the TE4D. Furthermore, the medical burden was assessed with the Cumulative Illness Rating Scale, modified version for Geriatrics [21], rating chronic medical burden from 14 organ systems. Information was obtained from medical history, physical examination as well as the available laboratory tests. A total score was computed by adding the subscores of each organ system except the psychiatric/behavioral system. Axis I diagnoses were established using DSM-IV criteria during a consensus conference attended by at least 3 faculty psychiatrists.

Patients were required to meet DSM-IV criteria for unipolar major depression by the Structured Clinical Interview for Axis I DSM-IV Disorders. Exclusion criteria included the history of other psychiatric disorders than depression (except personality disorders), alcohol or drug abuse or dependence, neurological illness which could eventually affect cognitive function (i.e., dementia or delirium according to DSM-IV criteria), current or unstable medical illness, stable medical illness or disability that could prevent the participant from completing the tasks or could directly affect cognitive functioning (i.e., past head injury), chronic disease such as syphilis that could affect cognitive function, MMSE score <24, DemTect <9 and/or TE4D dementia section ≤35. Individuals on any kind of ongoing vitamin substitution were excluded from the study. All patients were on psychiatric medication at the time of

neuropsychological testing and homocysteine determination. Nine patients were treated with selective serotonin reuptake inhibitors, 27 with serotonin-norepinephrine reuptake inhibitors, 18 with mirtazapine and 5 with tricyclic antidepressants. Twelve patients were on medication with atypical antipsychotics (olanzapine or quetiapine) and 1 with lorazepam. Eleven were on monotherapy, 19 were receiving mirtazapine and selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, 4 atypical antipsychotics and serotonin-norepinephrine reuptake inhibitors and 5 atypical antipsychotics and selective serotonin reuptake inhibitors. Lorazepam was combined with mirtazapine and a selective serotonin reuptake inhibitor in 1 patient.

Control subjects were free of significant unstable medical illnesses and not on medication deemed to affect cognition. After evaluation, which included a psychiatric examination, medical history, functional assessment and neuropsychological testing with MMSE, DemTect and TE4D, they were judged to be mentally healthy and to have an unimpaired global cognitive function and activities of daily living.

Cognitive Assessment

The cognitive assessment utilized well-established neuropsychological tests that covered cognitive domains relevant to understanding late-life depression.

Language Processing. The first part of the Stroop Color-Word Interference Test [22], consisting of reading color names, printed with black ink, was employed to assess language processing [23]. The time in seconds the participant needed to complete the task was measured.

Processing Speed. Processing speed was measured with the second task of the Stroop Test, in which the subjects have to name the color (blue, green or red) of a series of printed dashes [23]. The time in seconds needed for completing the task was counted.

Concentration. To measure concentration performance the d2 Test of Attention [24] was used. In this timed test, subjects are asked to cross out the letter 'd' each time it occurs with two dashes (above, below, or on both sides), arranged in several rows and containing distractors. The test variable was the concentration performance value (KL), which is calculated by subtracting the number of wrongly marked letters from the number of correctly marked letters.

Attention. The last part of the Stroop Test was used to measure selective attention [23]. In this part, participants had to identify the ink color of words, while they had to ignore the interfering word meaning (e.g. the word 'red' printed in green letters). The time needed for naming the printing inks of the color words was measured.

Homocysteine Laboratory Measurements

Fasting venous blood samples were collected a day after neuropsychological testing from all participants by venipuncture, were kept on ice and processed within 1 h of collection. Serum was stored at -20°C. Serum homocysteine was determined with a commercially available microplate enzyme immunoassay, using a Bio-Rad kit (Bio-Rad, Inc., Hercules, Calif., USA).

The study protocol was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki. All subjects provided written informed consent after complete description of the study.

Statistical Analyses

Normal distribution of data was checked using the Kolmogorov-Smirnov test. Statistical comparisons of demographic data between groups were performed by t test or by the Mann-Whitney U test and Kruskal-Wallis test for ordinal data and χ^2 test for nominal (categorical) data. Analysis of covariance was employed to examine the significance of interactions between variables. Both patients and the control group were split into participants with normal homocysteine ($\leq 11.7 \mu\text{mol/l}$) and individuals with high levels of homocysteine ($> 11.7 \mu\text{mol/l}$), according to Ubbink et al. [25], who proposed a reference range based on a mathematical prediction model. The Mann-Whitney U test or a t test was employed to examine the differences in age, education and in cognitive performance between patients with high homocysteine levels and patients with homocysteine concentrations $\leq 11.7 \mu\text{mol/l}$. Such an analysis was also performed in the control group. Possible associations between homocysteine levels as continuous variable and cognitive performance were investigated using multiple linear regression analyses. A p value of < 0.05 was considered to indicate statistical significance. Statistical analyses were implemented in SPSS 16.0 for Windows (SPSS, Chicago, Ill., USA).

Results

Demographics and Clinical Data (table 1)

Patients with depression were older and had fewer years of education compared to the control group ($t = -2.059$, $p = 0.044$ and $Z = -2.792$, $p = 0.005$, respectively). To avoid the influence of differences in age and education, 25 depressed patients were selected for comparison analyses of the performance of the two groups. For each healthy participant a patient with the same or nearly the same age and length of education was selected. The selection process was blind to the results of neurocognitive assessment. The differences in cognitive performance and in the magnitude of depressive symptoms between the selected patients (depression subgroup, $n = 25$) and the rest of patients ($n = 15$) did not reach statistical significance (language processing: $t = 0.635$, $p = 0.529$, processing speed: $t = 0.427$, $p = 0.672$, concentration: $t = -1.259$, $p = 0.216$, attention: $t = 1.610$, $p = 0.116$, Hamilton Depression Scale scores: $Z = -1.036$, $p = 0.300$, depression section of the TE4D scores: $t = 1.647$, $p = 0.108$, motor agitation and retardation symptoms: $Z = -1.540$, $p = 0.123$). The depression subgroup and the control group were homogeneous with respect to age ($t = 0.258$, $p = 0.797$), gender (χ^2 Fisher's exact test, $p = 1.000$), education ($Z = -1.453$, $p = 0.146$) and to the number of individuals with high levels of homocysteine ($> 11.7 \mu\text{mol/l}$) (χ^2 Fisher's exact test, $p = 0.252$). In line with our expectations, the analyses revealed differences between healthy participants and the depression subgroup in depressive

Table 1. Summary of demographic clinical and neuropsychological data and homocysteine levels (mean and standard deviation) for the group of elderly mentally healthy participants, the group of patients with geriatric depression and the subgroup of depressed patients included in the comparison¹

	Control group (n = 25)	Depression group (n = 40)	Depression subgroup (n = 25)
<i>Demographic characteristics</i>			
Age, years	69.44 ± 5.14	72.50 ± 6.21*	69.84 ± 5.80
Education, years	12.64 ± 1.82	11.88 ± 2.20*	11.25 ± 2.15
Sex (male/female)	9/16	8/32	8/17
<i>Clinical/diagnostic data</i>			
DemTect	15.68 ± 1.82	14.05 ± 2.36	14.16 ± 2.61
MMSE	26.68 ± 1.63	26.68 ± 1.62	26.68 ± 1.63
TE4D			
Depression	3.00 ± 2.12	12.98 ± 2.91	12.40 ± 2.68*
Dementia	43.96 ± 3.52	42.50 ± 3.26	42.28 ± 3.14
Hamilton Depression Scale	2.08 ± 1.66	18.12 ± 6.56	17.12 ± 5.37*
MARS	19.08 ± 0.40	30.50 ± 6.57	29.16 ± 5.77*
CIRS-G scales			
Total score	6.12 ± 2.35	5.82 ± 2.33	5.88 ± 2.35
Heart disease score	0.48 ± 0.71	0.82 ± 0.71	0.72 ± 0.79
Vascular disease score	1.40 ± 0.65	1.55 ± 0.60	1.60 ± 0.65
Homocysteine, µmol/l	11.32 ± 4.87	14.02 ± 6.47	13.30 ± 5.48
Number of participants with homocysteine levels >11.7 µmol/l	8	21	13
<i>Neuropsychological assessment</i>			
d2 concentration performance	132.84 ± 23.02	118.62 ± 30.52	122.64 ± 35.88
Stroop word naming, s	34.56 ± 4.93	43.18 ± 8.36	42.52 ± 8.24*
Stroop color naming, s	41.80 ± 5.33	52.65 ± 10.02	52.12 ± 9.79*
Stroop attention, s	97.56 ± 10.64	103.32 ± 17.39	105.75 ± 14.78

CIRS-G = Cumulative Illness Rating Scale for Geriatrics; MARS = Motor Agitation and Retardation Scale.

¹ The depression subgroup consisted of patients with depression who were selected from the depression group for the comparison of cognitive performance between controls and depressed patients, since the depression group and the control group differed significantly in age and education. * p ≤ 0.05 compared to the control group.

symptomatology as measured both with the Hamilton Depression Scale ($Z = -6.074$, $p < 0.0001$) and the depression section of the TE4D ($Z = -6.081$, $p < 0.0001$) as well as in motor agitation and retardation symptoms ($Z = -6.401$, $p < 0.0001$). No differences were detected between the groups in homocysteine concentration ($Z = -1.359$, $p = 0.174$), though homocysteine levels tended to be higher in depressed patients (table 1). No significant differences in homocysteine levels were found between men and women, neither for patients nor for healthy participants [control group: $t = 0.524$, $p = 0.605$, depression group ($n = 40$) $Z = -0.897$, $p = 0.370$, depression subgroup ($n = 25$): $t = -0.605$, $p = 0.551$].

Cognitive Performance

The subgroup of patients with depression was slower than the control group in language processing ($Z = -3.323$, $p = 0.001$) and in processing speed ($Z = -3.715$, $p < 0.0001$). Performance in concentration and attention did not differ between the groups ($t = -1.197$, $p = 0.238$ and $t = 1.413$, $p = 0.164$, respectively).

Homocysteine and Cognitive Performance in Geriatric Depression

Depressed patients with high levels of homocysteine ($>11.7 \mu\text{mol/l}$) and those with homocysteine concentrations $\leq 11.7 \mu\text{mol/l}$ did not differ significantly in education ($Z = -0.098$, $p = 0.922$). However, the subgroup with

high levels of homocysteine was older than the group of patients with low homocysteine ($t = -2.158$, $p = 0.037$). Therefore, we performed an analysis of covariance with language processing or processing speed scores as dependent variable, homocysteine levels as fixed factor and age as covariate. This analysis did not reveal an interaction between age and homocysteine levels (partial $\eta^2 = 0.680$, $p = 0.383$, and partial $\eta^2 = 0.752$, $p = 0.258$, respectively). Patients with high plasma homocysteine levels performed significantly better than patients with homocysteine concentrations $\leq 11.7 \mu\text{mol/l}$ in both language processing ($t = 2.975$, $p = 0.005$) and processing speed ($t = 2.963$, $p = 0.005$), whilst in the control group individuals with high homocysteine levels tended to perform worse than the rest of healthy participants ($t = -2.313$, $p = 0.03$, $t = -1.888$, $p = 0.089$, respectively).

To investigate further a possible positive association between homocysteine levels and cognitive performance in language processing and processing speed, the scores of depressed patients in the language processing and processing speed tasks were separately fed as dependent variables into a multiple linear analysis model which included homocysteine concentrations (continuous variable), age, sex, education and severity of depressive symptoms (Hamilton Depression Scale scores) as explanatory parameters. Only homocysteine levels were associated with performance in language processing (d.f. = 5, model's significance $p = 0.025$, standardized partial regression coefficient = -0.526 , $p = 0.002$) and in processing speed (d.f. = 5, model's significance $p = 0.032$, standardized partial regression coefficient = -0.514 , $p = 0.002$). These findings indicate a positive association between homocysteine concentration and cognitive performance since the longer the time needed for completing the tasks, the lower the performance. Such an analysis in the group of healthy participants did not reveal an impact of homocysteine concentration on the aforementioned cognitive domains (language processing: d.f. = 5, model's significance $p = 0.322$, standardized partial regression coefficient = -1.314 , $p = 0.204$, processing speed: d.f. = 5, model's significance $p = 0.501$, standardized partial regression coefficient = -0.250 , $p = 0.245$).

Discussion

The present study investigated possible associations between homocysteine and performance in cognitive domains in which differences between a group of mentally healthy elderly individuals and patients with late-onset depression were detected.

In the present study, patients with geriatric depression were characterized by decreased performance in language processing and slower processing speed in comparison to mentally healthy elderly individuals. The findings across studies that included both a comprehensive assessment of cognitive function and a group of healthy individuals are not in full agreement [26], probably because of differences among the study designs in methodological aspects, such as variations in age, severity of depressive symptoms as well as sample sizes etc. Our observations are in general agreement with the findings of Hart et al. [27] and Kramer-Ginsberg et al. [28], who found deficits in information processing speed in elderly depressed patients, as well as with the data of Butters et al. [29], who showed that late-life depression is characterized by slowed information processing. Surprisingly, no differences between patients with late-onset depression and controls in concentration and attention tasks were detected in our sample. Nonetheless, Butters et al. [29], who also assessed executive function with the Stroop Test, found no significant differences.

Homocysteine levels did not differ significantly across the groups, although homocysteine concentrations were higher in depressed patients. This finding is inconsistent with the significant differences detected in other studies [30–32]. The discrepancy could arise from differences in the features of the study groups. Our sample was carefully screened to preclude very mild dementia, a clinical entity associated with elevated homocysteine levels [9], whereas the study by Almeida et al. [30] and the Rotterdam Study [31] did not exclude patients with beginning dementia. Another possible interpretation of this discrepancy is the vascular disease burden. Elevated plasma concentrations of homocysteine in elderly patients with mental illness suggest the presence of vascular disease and may not be related to a specific clinical psychiatric diagnosis [33]. In our sample, the assessment of vascular and heart disease burden with the Cumulative Illness Rating Scale, modified version for Geriatrics, did not show differences across the groups (table 1); as a result, no differences in homocysteine levels between the groups were observed.

The findings of this study indicate that elevated homocysteine levels are associated with higher performance in language processing and processing speed in patients with late-onset depression. Our observations and the growing evidence that elevated homocysteine levels are associated with decreased global cognitive performance in demented and nondemented elderly patients and during alcohol withdrawal [8–14] seem to stand in contrast.

This contrast could be due to the great variability of neurocognitive tests utilized and the cognitive domains examined in the different studies. Moreover, it is noteworthy that due to differences in the characteristics of the samples, the findings of Bell et al. [14], who did not exclude patients with dementia from the geriatric depression sample, cannot be compared with our observations. The discrepancy might also arise from differences in specific neurobiochemical alterations, manifesting in each neuropsychiatric condition, especially in the light of the disturbances of glutamatergic transmission in the central nervous system that have recently been detected in the course of major depression [34, 35]. Alterations in the levels of N-methyl-D-aspartate receptor subunits NR1, NR2A, NR2B and their anchoring protein PSD-95 in subjects with major depression alter the specific properties of N-methyl-D-aspartate receptors such as binding affinities for agonists and antagonists and differences in conductance properties, since they are shaped by the combination of NR1 and NR2 subunits [36, 37]. Moreover, increasing evidence indicates that major depressive disorder is associated with perturbations in the metabolism of glutamate. Prefrontal glutamate/glutamine concentrations are abnormally decreased [38]. Reduction of glutamate levels has been observed in the anterior cingulate gyrus [39, 40], in dorsolateral prefrontal brain regions [41] and amygdala/hippocampus [42] of adults with major depression relative to controls, and these differences are not contingent on drug effects. In the presence of the above-mentioned alterations in glutamatergic transmission and low glutamate/glutamine levels, homocysteine substitutes glutamate in excitatory synapses and, as a result, can ameliorate deficits in language processing and processing speed in patients with geriatric depression [15]. It is of note that elevated homocysteine levels have been associated with better short- and long-term verbal memory performance in females with anorexia nervosa and bulimia nervosa [15]. A significant reduction in glutamate/glutamine levels has also been observed in anorectic patients [43].

It should be underscored that the current picture suggesting an association between homocysteine and language processing and processing speed in geriatric depression does not establish any straightforward facilitatory causal effect of homocysteine on cognitive function in geriatric depression, especially in the light of the absence of differences in homocysteine levels across the groups of healthy participants and patients with depression. Moreover, it is noteworthy that the definition of high concentrations of homocysteine according to Ub-

bink et al. [25], being associated with an increased risk for premature vascular disease, is clearly broader than that of the homocysteine levels which are usually referred as hyperhomocysteinemia in the literature [44].

A possible limitation of this study is the confounding effect of pharmacotherapy, which might have biased our results, since patients were on psychotropic medication at the time of neuropsychological testing and homocysteine sampling. Nevertheless, cognitive deficits in geriatric depression persist even after response to antidepressant medication and remission of mood symptoms [4, 45, 46]. To rule out any influence of medication, the sample of depressed patients was divided into six subgroups according to medications and combination of medications received. The subgroups did not differ with regard to age (Kruskal-Wallis test: $p = 0.801$), education (Kruskal-Wallis test: $p = 0.453$) and to homocysteine levels (Kruskal-Wallis test: $p = 0.755$). No significant differences among the groups in language processing (Kruskal-Wallis test: $p = 0.970$), processing speed tasks (Kruskal-Wallis test: $p = 0.981$), in concentration (Kruskal-Wallis test: $p = 0.955$) and attention tests (Kruskal-Wallis test: $p = 0.888$) were detected. Thus, a bias due to medication in the present study can in effect be ruled out. Other potential shortcomings of this study are the limited assessment of cognitive functions and the relatively small size of the sample. A further limitation concerns the interval between blood collection for homocysteine determination and the neurocognitive examination. However, homocysteine concentration is relatively constant over at least 1 month [47], and the interval in this study was only 1 day.

In conclusion, the present study shows first evidence of an association between homocysteine and language processing and processing speed in patients with geriatric depression. Further investigations, employing an extended neuropsychological assessment and modern functional imaging methods (i.e., a proton magnetic resonance spectroscopy) measuring glutamate/glutamine levels in the brain, are necessary to verify the role of homocysteine in strengthening brain resistance against the development of cognitive dysfunction in geriatric depression. Such investigations might solve the puzzle of homocysteine and cognition in late-onset depression and lead the way to future psychopharmacological interventions.

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