Memantine improves semantic memory in patients with amnestic mild cognitive impairment: A single-photon emission computed tomography study

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Abstract
Objective: This study was performed to assess the efficacy of memantine in patients with amnestic mild cognitive impairment (aMCI).
Methods: Thirty healthy controls and 45 patients diagnosed with aMCI based on the Petersen criteria were classified into 3 groups. Group 1 comprised patients who received a single memantine dose following examination (n = 25), Group 2 comprised patients who did not receive memantine treatment following examination (n = 20), and Group 3 comprised healthy age-matched volunteers (n = 30). Neuropsychological testing was performed, and the response to memantine was examined at baseline and at 12, 24, and 48 weeks. Single-photon emission computed tomography was performed at baseline and at 48 weeks in patients who received memantine treatment.
Results: Memantine treatment significantly improved the symptoms of aMCI according to the Wechsler Adult Intelligence Scale-Revised vocabulary subtest, backward digit span, and Blessed Dementia Rating Scale, all of which were recorded for the duration of the study.
Conclusion: These data indicate that patients with aMCI receiving memantine develop an improved semantic memory compared with no treatment. Further studies including larger patient cohorts are necessary to validate these findings.

Keywords
Memantine, dementia, amnestic mild cognitive impairment, computed tomography, Alzheimer's disease, Petersen's criteria

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Introduction

Mild cognitive impairment (MCI) is defined as the transitional phase between normal cognitive aging and dementia. This impairment is common, and nearly 19.0% of individuals aged >65 years are affected. Compared with older individuals with normal cognition, patients with MCI have a three- to five-times higher risk of developing Alzheimer’s disease (AD). Petersen’s criteria are frequently used to divide MCI into two groups: the amnestic (aMCI) and non-amnestic (naMCI) forms. Interestingly, aMCI is associated with frequent memory loss and progression to AD.1–3 However, patients with naMCI develop memory loss as well as other cognitive issues, including Lewy body dementia. Both types can be subcategorized; in the present study, however, we did not perform subcategorization because of the limited sample size.4,5 While the US Food and Drug Administration has approved several medications for the treatment of AD, no medications have been approved for patients with MCI.6

The importance of the glutamatergic N-methyl-D-aspartate (NMDA) receptor in memory and learning processes is well recognized. Memantine, a low-affinity non-competitive NMDA receptor antagonist, is the only glutamatergic drug approved for the treatment of moderate to severe cognitive symptoms of AD. Recent studies have shown that memantine can also reduce the levels of amyloid β peptides, which inhibit the amyloid β oligomer and improve cognitive performance.7,8 Memantine can usually be used in addition to acetylcholinesterase inhibitors in patients with AD9 Interestingly, memantine treatment results in slight beneficial effects on memory, activities of daily living, and behavior.

We conducted a prospective open-label study to test the hypothesis that the anti-glutamatergic activity of memantine can improve cognitive functioning. Patients with aMCI were treated with and without memantine and compared using neuropsychiatric tests and single-photon emission computed tomography (SPECT).

Material and methods

Participants

The present study was a 48-week, open-label extension study involving 45 patients diagnosed with aMCI and 30 healthy controls who were consecutively examined at the Memory and Dementia Outpatient Clinic of our neurology department. Volunteers who responded to the advertisements for this study underwent a multi-stage screening procedure. The inclusion criteria were an age of >55 years (with the exception of seven individuals aged 55–68 years); availability of an informant who could provide information about the participant’s daily function; absence of significant underlying medical, neurological, or psychiatric illness; and willingness to participate in the study procedures. All patients were required to be either cognitively normal or mildly impaired, but without dementia; that is, they were required to have a Clinical Dementia Rating (CDR) of either 0.0 or 0.5. All patients with MCI experienced memory that deviated from their previous normal function. We based the diagnosis of aMCI on the following criteria established by the International Working Group on Mild Cognitive Impairment10:

All participants were evaluated for depression using the 15-item short version of the Geriatric Depression Scale (GDS), in which a total score of >5 indicates depression. Neuropsychological testing was performed at baseline (week 0) and at 12, 24, and 48 weeks.

In total, 75 participants were included in the study (Group 1, n = 25; Group 2, n = 20; Group 3, n = 30). Group 1 comprised patients diagnosed with aMCI who received memantine. They initially received memantine at 5mg once daily, and this was
increased weekly by 5 mg/day in divided doses to a total dosage of 20 mg/day. Group 2 comprised patients diagnosed with aMCI who received no treatment. Group 3 comprised healthy controls without aMCI.

The exclusion criteria were as follows: probable or possible AD; the presence of other neurodegenerative conditions, such as parkinsonian, frontal, vascular, or metabolic dementia; a history or diagnosis of other neurologic diseases, such as stroke or hydrocephalus; a primary psychiatric diagnosis, such as depression or schizophrenia; the presence of sedating medications at the time of testing; and a metabolic or systemic disorder that might influence cognitive performance.

All participants underwent magnetic resonance imaging or brain computed tomography examinations, medical and neurological examinations, and neuropsychological testing by the same researchers. The following laboratory tests for dementia were requested: complete blood counts, blood chemistry, serum vitamin B12 and folic acid levels, thyroid function tests, and syphilis serology.

SPECT was performed at baseline and at 48 weeks in patients receiving memantine treatment.

**Neuropsychological tests**

The Mini-Mental State Examination (MMSE)\textsuperscript{11} was applied to all patients and controls by an experienced neurologist to evaluate the status of cognitive decline. All patients underwent neuropsychiatric evaluation including the digit span (forward and back), Wechsler Memory Scale subtests (immediate word recall list, delayed word recall, delayed word recognition, visual copy, and visual memory),\textsuperscript{12} Wechsler Adult Intelligence Scale-Revised (WAIS-R) vocabulary subtest, Boston Naming Test (BNT),\textsuperscript{13} clock drawing test,\textsuperscript{14} verbal fluency, Blessed Dementia Rating Scale (BDRS),\textsuperscript{15} Instrumental Activities of Daily Living scale,\textsuperscript{16,17} CDR,\textsuperscript{18} and GDS.\textsuperscript{19}

The same person implemented the neuropsychological tests for all patients. Sessions were conducted in the morning in a quiet room and lasted for 45 to 60 minutes.

**Perfusion SPECT imaging**

Regional cerebral blood flow was studied at baseline using SPECT. Patients received an injection of technetium-99 m ethyl cysteinate dimer and rested for 1 h in a quiet environment with their eyes closed. SPECT image acquisitions were performed using a double-head rotating gamma camera (Siemens) equipped with a fan beam collimator. SPECT was carried out at baseline and at 48 weeks in patients receiving memantine treatment.

**Semantic memory**

WAIS-R, word list memory, and recall. Semantic memory was assessed with the WAIS-R and word list memory recall. Free recall and recognition were assessed with a word list comprising 10 unrelated concrete nouns. Unit-weighted composite scores were computed based on vocabulary and general knowledge tasks.

**Ethics statement**

All patient examinations were conducted in full compliance with the Helsinki Declaration. All patients were informed before providing written consent, and the local ethics committee approved the research.

**Statistical analysis**

Statistical analyses were performed using SPSS for Windows 13.0 and Sigma Stat 3.1. The Shapiro–Wilk test was used to verify data normality assumptions. For normally distributed data, the paired sample t-test and
one-way analysis of variance were used for further analyses. For non-normally distributed data, the Wilcoxon t-test and Kruskal–Wallis test were used. For multiple comparisons, Dunn’s method and Tukey’s test were performed. A p-value of <0.05 was considered significant.

Multiple linear regression analysis was performed to identify independent associations of the cerebral SPECT values by including the parameters correlated with cerebral SPECT perfusion in the bivariate analysis. Standardized b regression coefficients and their significance according to the multiple linear regression analysis were reported. A p-value of <0.05 was considered statistically significant.

Results

Demographic data of all participants, including age, sex, educational status, and hand dominance, are summarized in Table 1. There was no significant difference among the three groups.

No significant differences were observed in any scores between Groups 1 and 2. However, there was a significant difference in the neuropsychiatric test scores between the patient groups and control group. At baseline, significant differences in calculation, word list memory-3, word list recall, WAIS-R, backward digit span, and BDRS scores were observed between the patient and control groups (p < 0.05) (Table 2).

At week 12, Group 1 had significantly improved scores on the MMSE, word list memory-2, word list recall, BNT, and CDR compared with Group 3. Improvement in the MMSE score was observed in Group 1, while no significant improvement was found in Groups 2 and 3 compared with baseline. Word list recall scores were increased in all groups, especially Group 1. Interestingly, a statistically significant advancement was observed for the calculation scores in Groups 1 and 2. The BNT and BDRS scores were significantly improved only in Group 1 (Table 3).

The MMSE scores were higher at week 24 than at week 12 in Groups 1 and 2. At week 24, Group 1 showed significantly higher scores for word list memory-3, word list recall, WAIS-R, backward digit span, BDRS, and GDS compared with baseline. Group 2 showed a statistically significant decrease in verbal fluency scores at week 24 (Table 3).

At week 48, the significant increase in the word list memory-3, word list recall, WAIS-R, backward digit span, BDRS, and GDS scores continued. No differences were observed in the other test scores among the three groups (Table 3).

Semantic memory composite Z-score

Z-scores were measured for the WAIS-R and word list recall test, which were used for semantic memory. The scores were

| Table 1. Demographic characteristics of the study groups. |
|----------------------------------------------------------|
| **Group 1**                  | **Group 2**                  | **Group 3**                  | **p value** |
| (n = 25)                    | (n = 20)                     | (n = 30)                     |             |
| Age (years)                 | 65.0 ± 8.04                  | 66.3 ± 7.40                  | >0.05       |
| Hand dominance (right/left) | 25/0                          | 19/1                          | >0.05       |
| Educational status          | 21/4                          | 17/3                          | >0.05       |
| (educated/uneducated)       |                               |                               |             |
| Sex (female/male)           | 14/11                         | 11/9                          | >0.05       |

Data are presented as mean ± standard deviation or n.
compared before and after treatment. Z-scores were higher in the memantine-treated group.

**Correlation with SPECT perfusion**

According to the results of the bivariate analysis, semantic memory was significantly associated with the right superior frontal cortex (r = 0.167, p = 0.020), left superior frontal cortex (r = 0.165, p < 0.001), right medial frontal cortex (r = 0.224, p = 0.002), left medial frontal cortex (r = 0.221, p = 0.024), right inferior frontal cortex (r = 0.211, p = 0.024), left inferior frontal cortex (r = 0.218, p = 0.023), right superior parietal cortex (r = 0.215, p = 0.020), left superior parietal cortex (r = 0.224, p = 0.020), right inferior parietal cortex (r = 0.218, p = 0.022), left inferior parietal cortex (r = 0.214, p = 0.023), right superior temporal cortex (r = 0.184, p = 0.020), left superior temporal cortex (r = 0.176, p = 0.020), right inferior temporal cortex (r = 0.189, p = 0.011), and left inferior temporal cortex (r = 0.198, p = 0.023). Multiple linear regression analysis showed that the semantic memory Z-score was significantly associated with SPECT perfusion in the right inferior temporal cortex (b = 0.192, p = 0.010).

The multiple linear regression analysis showed that the semantic memory Z-score was significantly associated with SPECT perfusion in the right inferior temporal cortex (b = 0.192, p = 0.010).

A statistically significant difference was found in the right inferior temporal cortex (p = 0.031) in SPECT performed at the beginning of the study and at about 48 weeks in Group 1. This difference was characterized by an increase in perfusion around 48 weeks in these regions (Table 4). No significant difference in cerebral perfusion was observed between Groups 2 and 3 at the beginning of the study or at 48 weeks.

### Table 2. Baseline neuropsychologic test scores in patients with MCI.

| Baseline                  | Group 1 (n = 25) | Group 2 (n = 20) | Group 3 (n = 30) | p value |
|---------------------------|------------------|------------------|------------------|---------|
| MMSE                      | 27.1 ± 1.9 (27)  | 27.3 ± 2.3 (27)  | 28.6 ± 2.5 (28)  | 0.21    |
| Wechsler memory scale     |                  |                  |                  |         |
| -Word list memory-1       | 5.3 ± 1.5 (5)    | 5.2 ± 1.9 (5)    | 5.8 ± 1.1 (6)    | 0.08    |
| -Word list memory-2       | 5.4 ± 1.2 (5)    | 5.6 ± 1.8 (5)    | 5.9 ± 1.2 (6)    | 0.07    |
| -Word list memory-3       | 6.2 ± 1.3 (6)    | 6.1 ± 2.1 (6)    | 7.9 ± 0.09 (7.5) | 0.06    |
| -Word list recall         | 4.1 ± 2.1 (4)    | 4.4 ± 1.6 (4.4)  | 5.9 ± 1.9 (5.5)  | 0.04    |
| -Word list recognition    | 18.2 ± 1.9 (18)  | 19.4 ± 1.1 (19)  | 19.8 ± 1.3 (19.5)| 0.03    |
| Constriction Ability      | 10.3 ± 2.5 (10.5)| 11.0 ± 0.0 (11)  | 11.0 ± 0.0 (11)  | 0.04    |
| Calculation               | 3.4 ± 3.8 (3.5)  | 3.6 ± 1.8 (3.6)  | 5.0 ± 0.0 (5)    | 0.02    |
| Verbal fluency            | 18.2 ± 3.6 (18)  | 18.6 ± 3.2 (18)  | 20.3 ± 4.2 (20)  | 0.07    |
| Backward Digit Span       | 3.6 ± 1.5 (3.5)  | 3.4 ± 2.9 (3.4)  | 4.3 ± 1.5 (4)    | 0.03    |
| BNT                       | 13.7 ± 1.9 (14)  | 13.6 ± 1.8 (14)  | 13.8 ± 2.1 (14)  | 0.41    |
| CDT                       | 5.6 ± 1.2 (5.5)  | 5.4 ± 1.6 (5.5)  | 5.8 ± 1.1 (6)    | 0.08    |
| BDRS                      | 1.16 ± 1.3 (1)   | 1.14 ± 1.9 (1)   | 017.9 ± 2.0 (0.5)| 0.004   |
| IADL                      | 15.6 ± 1.8 (15.5)| 15.8 ± 1.4 (15.5)| 16.4 ± 1.9 (16)  | 0.08    |
| CDR                       | 0.5 ± 0.0 (0.5)  | 0.5 ± 0.0 (0.5)  | 0.0 ± 0.0 (0.0)  | 0.02    |
| GDS                       | 7.1 ± 1.2 (7.1)  | 6.9 ± 1.4 (7)    | 7.6 ± 2.2 (7.4)  | 0.06    |
| WAIS-R                    | 53.8 ± 7.4 (53.8)| 54.2 ± 6.7 (54.1)| 60.2 ± 2.4 (60)  | 0.004   |

Data are presented as mean ± standard deviation (median).
| Scale                          | Baseline     | Week 12     | Week 24     | Week 48     | p value |
|--------------------------------|--------------|-------------|-------------|-------------|---------|
| MMSE                          |              |             |             |             |         |
| Group 1                        | 27.1 ± 1.9   | 29.1 ± 0.01 | 29.1 ± 0.09 | 29.3 ± 1.2  | 0.034   |
| Group 2                        | 27.3 ± 2.3   | 28.7 ± 1.9  | 28.9 ± 1.7  | 29.2 ± 2.5  | 0.065   |
| Group 3                        | 28.6 ± 2.5   | 29.5 ± 1.1  | 29.5 ± 1.1  | 29.5 ± 1.1  | 0.075   |
| Word list memory-1             |              |             |             |             |         |
| Group 1                        | 5.3 ± 1.5    | 5.4 ± 1.2   | 5.4 ± 1.4   | 5.5 ± 1.2   | 0.075   |
| Group 2                        | 5.2 ± 1.9    | 5.2 ± 1.4   | 5.2 ± 1.9   | 5.4 ± 1.6   | 0.080   |
| Group 3                        | 5.8 ± 1.1    | 5.8 ± 1.6   | 5.9 ± 1.4   | 5.9 ± 1.8   | 0.085   |
| Word list memory-2             |              |             |             |             |         |
| Group 1                        | 5.4 ± 1.2    | 6.7 ± 2.2   | 6.3 ± 1.9   | 6.3 ± 1.5   | 0.042   |
| Group 2                        | 5.6 ± 1.8    | 5.9 ± 1.1   | 6.2 ± 1.0   | 6.1 ± 1.6   | 0.065   |
| Group 3                        | 6.3 ± 1.8    | 6.3 ± 2.1   | 7.2 ± 1.5   | 7.2 ± 1.5   | 0.068   |
| Word list memory-3             |              |             |             |             |         |
| Group 1                        | 6.2 ± 1.3    | 6.4 ± 1.1   | 6.7 ± 1.2   | 6.8 ± 1.5   | 0.035   |
| Group 2                        | 6.1 ± 2.1    | 6.7 ± 1.1   | 6.4 ± 1.0   | 6.3 ± 1.6   | 0.055   |
| Group 3                        | 7.6 ± 1.3    | 7.9 ± 2.2   | 8.1 ± 1.2   | 8.1 ± 1.3   | 0.027   |
| Word list recall               |              |             |             |             |         |
| Group 1                        | 4.1 ± 2.1    | 6.3 ± 1.6   | 6.5 ± 1.2   | 6.6 ± 1.5   | 0.035   |
| Group 2                        | 4.8 ± 1.6    | 6.4 ± 1.3   | 6.4 ± 1.6   | 6.5 ± 1.4   | 0.002   |
| Group 3                        | 5.9 ± 1.9    | 6.5 ± 1.3   | 7.8 ± 1.6   | 7.2 ± 1.3   | 0.009   |
| Word list recognition          |              |             |             |             |         |
| Group 1                        | 18.2 ± 1.9   | 20.3 ± 1.7  | 19.7 ± 1.1  | 19.8 ± 1.5  | 0.002   |
| Group 2                        | 19.4 ± 1.1   | 19.8 ± 1.7  | 19.9 ± 1.2  | 19.7 ± 1.4  | 0.067   |
| Group 3                        | 19.6 ± 1.3   | 19.8 ± 1.3  | 20.0 ± 0.0  | 20.0 ± 0.0  | 0.015   |
| WAIS-R                         |              |             |             |             |         |
| Group 1                        | 53.8 ± 7.4   | 54.3 ± 5.7  | 57.7 ± 5.4  | 57.8 ± 6.5  | 0.002   |
| Group 2                        | 54.2 ± 6.9   | 54.9 ± 4.7  | 55.1 ± 3.2  | 55.3 ± 5.4  | 0.067   |
| Group 3                        | 60.1 ± 2.4   | 60.2 ± 4.3  | 60.4 ± 5.0  | 60.4 ± 3.8  | 0.085   |
| Calculation                    |              |             |             |             |         |
| Group 1                        | 3.4 ± 2.9    | 4.6 ± 1.8   | 4.9 ± 1.5   | 4.9 ± 1.0   | 0.035   |
| Group 2                        | 3.9 ± 1.8    | 4.3 ± 1.2   | 4.6 ± 0.0   | 4.7 ± 1.0   | 0.056   |
| Group 3                        | 5.0 ± 0.0    | 5.0 ± 0.0   | 5.0 ± 0.0   | 5.0 ± 0.0   | 0.072   |
| Verbal fluency                 |              |             |             |             |         |
| Group 1                        | 18.2 ± 3.6   | 17.2 ± 2.1  | 18.2 ± 3.5  | 18.0 ± 5.0  | 0.056   |
| Group 2                        | 18.6 ± 3.2   | 17.8 ± 3.3  | 15.4 ± 3.2  | 15.0 ± 4.0  | 0.025   |
| Group 3                        | 20.3 ± 4.2   | 22.5 ± 3.5  | 21.8 ± 5.6  | 23.3 ± 6.2  | 0.052   |
| BNT                            |              |             |             |             |         |
| Group 1                        | 11.7 ± 1.9   | 13.6 ± 1.4  | 13.6 ± 1.5  | 14.5 ± 1.0  | 0.001   |
| Group 2                        | 13.6 ± 1.8   | 13.5 ± 1.2  | 13.6 ± 1.1  | 13.8 ± 1.0  | 0.065   |
| Group 3                        | 13.8 ± 2.1   | 14.1 ± 0.8  | 14.3 ± 1.0  | 14.4 ± 0.8  | 0.072   |
| BDRS                           |              |             |             |             |         |
| Group 1                        | 1.16 ± 1.3   | 1.12 ± 0.9  | 0.94 ± 1.4  | 0.85 ± 0.6  | 0.020   |
| Group 2                        | 1.14 ± 1.9   | 1.14 ± 1.2  | 1.11 ± 1.3  | 1.11 ± 1.0  | 0.070   |
| Group 3                        | 1.07 ± 2.0   | 1.08 ± 0.8  | 1.06 ± 1.2  | 1.06 ± 0.2  | 0.082   |
| GDS                            |              |             |             |             |         |
| Group 1                        | 7.1 ± 1.2    | 7.1 ± 0.9   | 7.4 ± 1.6   | 7.8 ± 1.0   | 0.025   |
| Group 2                        | 6.9 ± 1.4    | 7.2 ± 1.3   | 7.3 ± 1.7   | 7.3 ± 1.0   | 0.075   |
| Group 3                        | 7.6 ± 1.4    | 7.7 ± 0.8   | 7.6 ± 1.2   | 7.9 ± 0.6   | 0.082   |

Data are presented as mean ± standard deviation
Table 4. Cerebral SPECT values in patients with amnestic mild cognitive impairment treated with memantine (Group 1) (Wilcoxon signed ranks test).

| Location                       | Baseline          | Week 48          | p    |
|--------------------------------|-------------------|------------------|------|
| Superior frontal cortex        |                   |                  |      |
| Right                          | 2.68 (1.68–2.87)  | 2.74 (2.56–2.96) | 0.107|
| Left                           | 2.49 (1.66–3.03)  | 2.78 (2.53–2.93) | 0.286|
| Medial frontal cortex          |                   |                  |      |
| Right                          | 2.67 (1.55–2.93)  | 2.89 (2.67–3.13) | 0.25 |
| Left                           | 2.71 (1.54–3.10)  | 2.83 (2.68–2.98) | 0.133|
| Inferior frontal cortex        |                   |                  |      |
| Right                          | 2.56 (1.39–2.73)  | 2.68 (2.46–2.95) | 0.16 |
| Left                           | 2.43 (1.39–2.83)  | 2.67 (2.55–2.87) | 0.64 |
| Superior parietal cortex       |                   |                  |      |
| Right                          | 2.46 (1.40–2.67)  | 2.62 (2.45–2.87) | 0.58 |
| Left                           | 2.40 (1.39–2.75)  | 2.73 (2.19–2.90) | 0.23 |
| Inferior parietal cortex       |                   |                  |      |
| Right                          | 2.36 (1.40–2.72)  | 2.59 (2.44–2.72) | 0.006|
| Left                           | 2.33 (1.28–2.58)  | 2.61 (2.29–2.69) | 0.142|
| Superior temporal cortex       |                   |                  |      |
| Right                          | 2.57 (1.52–2.80)  | 2.69 (2.45–2.88) | 0.142|
| Left                           | 2.50 (1.35–2.79)  | 2.66 (2.46–2.72) | 0.324|
| Inferior temporal cortex       |                   |                  |      |
| Right                          | 2.67 (1.55–2.90)  | 2.82 (2.47–2.93) | 0.031|
| Left                           | 2.47 (1.54–2.84)  | 2.62 (2.36–2.80) | 0.387|
| Occipital cortex               |                   |                  |      |
| Right                          | 2.51 (1.40–2.69)  | 2.58 (2.33–2.87) | 0.58 |
| Left                           | 2.34 (1.57–2.73)  | 2.57 (2.36–3.02) | 0.70 |
| Thalamus                       |                   |                  |      |
| Right                          | 2.41 (1.43–2.67)  | 2.49 (2.31–2.57) | 0.952|
| Left                           | 2.21 (1.36–2.61)  | 2.45 (2.24–2.57) | 0.277|
| Cerebellum                     |                   |                  |      |
| Right                          | 3.04 (1.94–3.54)  | 3.39 (2.91–3.77) | 0.091|
| Left                           | 3.02 (1.92–3.69)  | 3.29 (3.07–3.69) | 0.107|

Data are presented as median (25th–75th percentiles).

Discussion

A previous study showed that the rate of progression to clinically diagnosable AD is 10% to 15% per year among persons who meet the criteria for the aMCI, in contrast to 1% to 2% per year among normal elderly persons. Early diagnosis is essential for disease prevention and the development of new treatment strategies. Detection of AD at a very early time point would enable early intervention and a timely start of therapy, possibly preventing disease progression.

Acetylcholinesterase inhibitors have long accounted for a majority of the treatments administered for MCI; this trend follows the cholinergic hypotheses. Another approach that is widely accepted (at least as widely accepted as the histopathogenesis of AD) is the glutaminergic hypothesis, which is related to the increased effect of glutamate. The discovery that the toxic effect of glutamatergic neurotransmission is present in the very early phases of the disease brought modulatory treatments up
to date. In the present study, we examined the effects of memantine on neuropsychological measures for aMCI, improvements in which could be mediated by a neuron-protective effect of memantine.

The current use of memantine aims to treat cognitive and behavioral disorders in patients with mild to moderately severe AD and mild to moderate vascular dementia. No pharmacological agents have obtained regulatory approval for the treatment or prevention of these disorders. A review of published clinical trials indicated that early treatment of hypertension, a risk factor for stroke, reduces the risk of vascular dementia and slows its progression. Because neuronal damage begins in the preclinical phase of the disease, it is believed that neuron-protective treatments should be initiated at very early stages.

The enhancing effects of NMDA receptor antagonists on cerebral blood flow have been demonstrated in experimental ischemic models. In a study of the efficacy of memantine on neuroimaging, glucose metabolism decreased to a lesser degree in the memantine than placebo group. This finding supports the functional and neuroprotective efficacy of memantine. Increased perfusion in the posterior parietal area, which affects attention and memory as shown by cerebral SPECT studies, has been observed in patients with AD treated with donepezil. Studies using functional imaging techniques have suggested that semantic memory impairment, which occurs relatively early in the course of AD, is caused by neural degeneration in the areas of association in the lateral and inferior temporal regions.

Currently, no drugs are specifically permitted by the US Food and Drug Administration for MCI. Because aMCI may be associated with AD, drug therapies targeting AD may be help to manage MCI. In one study, the combined treatment of galantamine and memantine had cognitive benefits in the short term, and cognitive decline occurred after discontinuation of galantamine. Although various studies have examined donepezil, rivastigmine, and galantamine alone or combination with memantine, reliable data on the influence of memantine alone in the treatment of aMCI are lacking.

In one related study involving 270 amnesic patients with MCI, Salloway et al. investigated the effectiveness of donepezil on memory loss by comparison with a placebo group. Although donepezil treatment was not strong enough to affect pure memory test scores (a primary scale of efficacy), it had positive effects on attention, concentration, and psychomotor speed. Other similar studies have suggested that donepezil treatment improves logical memory at week 24. In a study investigating the role of galantamine in patients with MCI, global rating scales improved and ADAS-cog subscale scores decreased after 6 weeks at all dose levels. In another study by Pelton et al., 35 patients received antidepressant and memantine treatment, which was found to be effective on cognition. The dementia conversion rate was significantly lower than in the control group.

In the present study, the recognition, word list memory and recall, WAIS vocabulary subtest, BDRS, and GDS scores differed between memantine-treated patients and controls; these scores decreased until they normalized at week 48. Similar results were observed for the MMSE and global assessment scale, for which the scores in memantine-treated patients increased at week 48 and the significant differences in the scores between these patients and the controls were no longer present. These results suggest that 48 weeks of memantine treatment improved patient functioning until their scores were comparable with those of the healthy controls, whereas this was not the case for patients with untreated aMCI. Indeed, no change was observed in the
global cognitive and functional scales of the patients with untreated aMCI. However, the memory test results showed improvement. The fact that fewer significant between-group differences were apparent over time between the patients not receiving memantine and the control group suggests that memory functions improved over time in the former. We found that patients not treated with memantine showed a deterioration of the GDS score. Therefore, memantine may reduce the risk of depression.

Semantic memory deficits are frequently seen in patients with AD, even in the early phase, but not necessarily in patients in the predementia state, as in aMCI. In the present study, we observed a significant improvement in the WAIS-R, word list memory, and recall test used to evaluate semantic memory at 48 weeks in patients who received memantine.

Memantine is a noncompetitive receptor antagonist, and it delays the process of dementia by preventing the pathological activation of NMDA receptors. Its neuroprotective effects have been displayed in various neurological disorders. Importantly, memantine reportedly reduces the release of proinflammatory factors in activated microglia.42,43

In patients with aMCI, pathologic damage first occurs in the medial temporal structures, mainly the entorhinal cortex, which causes episodic memory deficits.44 The present study showed a significant positive correlation between semantic memory and SPECT perfusion of the right inferior temporal region in patients receiving memantine. This finding may be due to the neuroprotective effects of memantine therapy in patients with aMCI.

Ramaswamy et al.45 observed improvement in memory, core symptoms of post-traumatic stress disorder, and depression in combat veterans with post-traumatic stress disorder after open-label treatment with memantine. One limitation of the present study is the relatively small number of participants. The low prevalence of aMCI restricted our ability to include a greater number of individuals. Another limitation is the duration of the study. A longer-term study would have allowed us to better observe the efficacy of memantine and determine which patients did and did not develop progression to AD or dementia.

We found a significant increase in the WAIS vocabulary subtest score when evaluating language functions and semantic memory in our study. SPECT revealed cerebral hyperperfusion in the right inferior temporal region in the memantine-treated patients before and 48 weeks after the start of treatment.

In conclusion, neuropsychological tests and cerebral SPECT imaging showed that memantine may be effective in improving the semantic memory of patients with aMCI. Memantine may inhibit oxidative stress and inflammation during the early stage of the disease. The optimal treatment for patients with MCI is controversial. Importantly, however, our study has shown that memantine can be used for initial therapy of MCI. Future studies should further investigate this topic by including greater sample sizes and performing long-term follow-up.

Ethics and consent
Our Clinical Research Ethics Committee approved the study (13 February 2011-90). All patients provided written informed consent.

Consent for publication
Consent for publication was obtained from all authors.

Data and materials availability
The dataset was available for all authors of the study.

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Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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References
1. Portet F, Ousset PJ, Visser PJ, et al. Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure: report of the MCI working group of the European consortium on Alzheimer’s disease. J Neurol Neurosurg Psychiatry 2006; 77: 714–718.
2. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004; 256: 183–194.
3. Petersen RC and Morris JC. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 2005; 62: 1160–1163.
4. Edmonds EC, Delano-Wood L, Galasko DR, et al. Alzheimer’s disease neuroimaging initiative. Subjective cognitive complaints contribute to misdiagnosis of mild cognitive impairment. J Int Neuropsychol Soc 2014; 20: 836–847.
5. Boyle PA, Wilson RS, Aggarwal NT, et al. Mild cognitive impairment Risk of Alzheimer disease and rate of cognitive decline. Neurology 2006; 67: 441–444.
6. Schmidtke K and Hermeneit S. High rate of conversion to Alzheimer’s disease in a cohort of amnestic MCI patients. Int Psychogeriatr 2008; 20: 96–108.
7. Myhrer T. Neurotransmitter systems involved in learning and memory in the rat: a meta-analysis based on studies of four behavioral tasks. Brain Res Rev 2003; 41: 268–287.
8. Peskind ER, Potkin SG, Pomara N, et al. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006; 14: 704–715.
9. Scarpini E, Scheltens P and Feldman H. Treatment of Alzheimer’s disease: current status and new perspectives. Lancet Neurol 2003; 2: 539–547.
10. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment- beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256: 240–246.
11. Folstein MF, Folstein SE and McHugh PR. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–198.
12. Wechsler D. Wechsler memory scale-revised manual. New York: Psychological Corporation, 1987.
13. LaBarge E, Edwards D and Knesevich JW. Performance of normal elderly on the Boston naming test. Brain Lang 1986; 273: 80–84.
14. Sunderland T, Hill JL, Mellow AM, et al. Clock drawing in Alzheimer’s disease. A novel measure of dementia severity. J Am Geriatr Soc 1989; 37: 725–729.
15. Blessed G, Tomlinsin B and Roth M. The association between quantitative measures of dementia and of senile change in the cerebral gray matter of elderly subjects. Brit J Psychiatry 1968; 114: 797–811.
16. Thal LJ, Grundman M and Golden R. Alzheimer’s disease: a correlational analysis of the blessed information-memory-concentration test and the mini-mental state exam. Neurology 1986; 36: 262–264.
17. Lawton MP and Brody EM. Assessment of older people: self maintaining and instrumental activities of daily living. Gerontologist 1969; 9: 179–186.
18. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140: 566–572.
impairment and the cholinergic hypothesis. Ann Neurology 2002; 51: 143–144.

22. Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008; 70: 2024–2035.

23. Palmer A and Gershon S. Is the neuronal basis of Alzheimer's disease cholinergic or glutamatergic? FASEB J 1990; 4: 2745–2752.

24. Muller W, Mutschler E and Riederer P. Noncompetitive NMDA receptor antagonists with fast open-channel blocking kinetics and strong voltage-dependency as potential therapeutic agents for Alzheimer's dementia. Pharmacopsychiatry 1995; 28: 113–124.

25. Winblad B, Jones RW, Wirth Y, et al. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomized clinical trials. Dement Geriatr Cognition Disorders 2007; 24: 20–27.

26. McShane R, Areosa Sastre A and Minakaran N. Memantine for dementia. Cochrane Database Syst 2006: CD003154.

27. Dogan A, Eras MA, Rao VL, et al. Protective effects of memantine against Ischemia-reperfusion injury in spontaneously hypertensive rats. Acta Neurochir (Wien) 1999; 141: 1107–1113.

28. Erlandsson K, Bressan RA, Mulligan RS, et al. Kinetic modelling of [123I] CNS 1261—a potential SPECT tracer for the NMDA receptor. Nucl Med Biol 2003; 30: 441–454.

29. Schmidt R, Ropele S, Pendle B, et al. Longitudinal multimodal imaging in mild to moderate Alzheimer disease: a pilot study with memantine. J Neurol Neurosurg Psychiatry 2008; 79: 1312–1317.

30. Rodriguez G, Vitali P, Canfora M, et al. Quantitative EEG and perfusional single photon emission computed tomography correlation during long-term donepezil therapy in Alzheimer disease. Clin Neurophysiol 2004; 115: 39–49.

31. Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 2010; 17: 1236–1248.

32. Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005; 352: 2379–2388.

33. Farlow MR. Treatment of mild cognitive impairment (MCI). Curr Alzheimer Res 2009; 6: 362–367.

34. Croisile B, Auriacombe S, Etchary-Bouyx F, et al. The new 2011 recommendations of the National Institute on aging and the Alzheimer’s Association on diagnostic guidelines for Alzheimer’s disease: Preclinical stages, mild cognitive impairment and dementia. Rev Neurol (Paris) 2012; 168: 471–482.

35. Loy C and Schneider L. Galantamine for Alzheimer’s disease and mild cognitive impairment. Cochrane Database Syst Rev 2004; 4: CD001747.

36. Peters O, Lorenz D, Fesche A, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. J Nutr Health Aging 2012; 16: 544–548.

37. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 2004; 63: 651–657.

38. Peter J, Kaiser J, Landerer V, et al. Category and design fluency in mild cognitive impairment: Performance, strategy use and neural correlates. Neuropsychologia 2016; 93: 21–29.

39. Liu Y, Cai ZL, Xue S, et al. Proxies of cognitive reserve and their effects on neuropsychological performance in patients with mild cognitive impairment. J Clin Neurosci 2013; 20: 548–553.

40. Langa KM and Levine DA. The diagnosis and management of mild cognitive impairment: a clinical review. JAMA 2014; 312: 2551–2561.

41. Pelton GH, Harper OL, Roose SP, et al. Combined treatment with memantine/escitalopram for older depressed patients with cognitive impairment: a pilot study. Int J Geriatr Psychiatry 2015; 11: 4375.

42. Cooper C, Li R, Lyketsos C, et al. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 2013; 203: 255–264.

43. Wang F, Zou Z, Gong Y, et al. Regulation of human brain microvascular endothelial cell adhesion and barrier functions by
memantine. *J Mol Neurosci* 2017; 62: 123–129. doi: 10.1007/s12031-017-0917-x

44. Starr JM, Loeffler B, Abousleiman Y, et al. Episodic and semantic memory tasks activate different brain regions in Alzheimer disease. *Neurology* 2005; 65: 266–269.

45. Ramaswamy S, Madabushi J, Hunziker J, et al. An open-label trial of memantine for cognitive impairment in patients with post-traumatic stress disorders. *J Aging Res* 2015; 2015: 934–962.