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学位申請論文

Effect of Memantine on Brain Metabolic Activity and Perfusion in Drug-naïve Moderate Alzheimer's Disease Patients

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Keywords: Alzheimer's disease, memantine, 18F-FDG, PET, 99mTc-ECD, SPECT, MMSE, NPI

Abstract

Objective: Memantine is a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist that improves or stabilizes cognitive impairment in moderate to severe Alzheimer's disease (AD). However, the effects of memantine on regional brain metabolic activity and perfusion are not fully known. To clarify these effects, we investigated the efficacy of memantine monotherapy using multimodal neuroimaging in drug-naïve patients with moderate AD.

Methods: This was a prospective open-labeled study of patients with drug-naïve moderate AD before and after 12 weeks of treatment with memantine, conducted between April 2015 and December 2016. Imaging was performed using 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) and 99mTc-ethyl cysteinate dimer-single photon emission computed tomography (99mTc-ECD-SPECT), to assess brain metabolic activity and perfusion, respectively. The imaging data, registered to a probabilistic anatomical atlas, were evaluated by voxel-based analysis.

Results: A total of 20 patients were enrolled and 17 patients' imaging datasets were analyzed. Brain regions with increased metabolic activity following memantine treatment in previously drug-naïve AD patients included a wide range of cerebral

cortexes, particularly the right inferior parietal lobule, right supramarginal gyrus, right angular gyrus, and right paracentral lobule ($p < 0.01$, paired t-test). Only small regions had increased brain perfusion ($p < 0.01$, paired t-test).

Conclusion: We believe this is the first study focusing on brain metabolic activity and perfusion in the same drug-naïve moderate AD patients before and after memantine treatment. There were inconsistencies between the regions with increased metabolic activity and perfusion after memantine treatment in drug-naïve AD patients, suggesting that brain metabolism may increase without a concurrent increase in blood perfusion. This study may help elucidate the mechanism of action of memantine.

Introduction

Alzheimer's disease (AD) is the most common dementia, and the development of drug therapies for AD have advanced in recent years. Based on the pathophysiology hypothesis of AD, two drug types, N-methyl-D-aspartate receptor (NMDAR) antagonists and cholinesterase inhibitors (ChEIs), have been used clinically in AD patients to date.

Memantine, the only noncompetitive NMDAR antagonist, has been used clinically, to improve or stabilize cognitive impairment in moderate to severe AD [1, 2]. However, the effects of memantine on regional brain metabolic activity and perfusion are not fully known.

Regional perfusion on single photon emission computed tomography (SPECT) is typically reduced in the parietal, temporal lobe, and posterior cingulate regions of AD patients [3-7]. 18F-fluorodeoxyglucose-positron emission tomography (18F-FDG-PET) measures regional cortical metabolic activity and has found that the metabolic rate in the parietal and temporal cortex is reduced early in the course of AD [8,9]. Cortical metabolism declines as Alzheimer's disease progresses [10-13].

It has been reported that the degree of uptake on 18F-FDG-PET and 99mTc-ethyl cysteinate dimer-SPECT (99mTc-ECD-SPECT) in patients with AD and mild cognitive

impairment shows significant correlations in the frontal, temporal, and parietal lobes. [14].

Many previous studies have measured perfusion and metabolic activity in AD patients treated with ChEIs. ChEIs treatment increases cortical blood flow in the frontal lobe [15, 16], the right anterior cingulate, the dorsolateral prefrontal, and the temporoparietal areas bilaterally [17]. Another study demonstrated that ChEIs preserve cortical blood flow in right middle temporal gyrus [18] and the occipital precuneus [19]. Treatment with ChEIs has a positive effect on cerebral metabolism in the frontal region [20]. However, no previous study has measured changes in regional brain perfusion in patients with AD before and after memantine treatment. Additionally, studies about brain metabolic activity measured by 18F-FDG-PET in AD patients treated with memantine are a few. Sultzer *et al.* reported that metabolic activity in the bilateral inferior temporal gyri and angular gyri and supramarginal gyri increased after 10 weeks of memantine treatment in patients with AD on stable ChEI medication [21]. However, no previous study has simultaneously examined 18F-FDG-PET and 99mTc-ECD-SPECT on the same drug-naïve AD patients after memantine treatment alone.

It remains to be clarified how change in brain metabolic activity and perfusion occurs in

previously drug-naïve AD patients after memantine treatment alone. Another question is whether the effects of memantine treatment assessed by brain functional imaging such as 99mTc-ECD-SPECT and 18F-FDG-PET are similar. To answer these questions, we investigated the efficacy of 12 weeks of memantine monotherapy using multimodal imaging (18F-FDG-PET and 99mTc- ECD-SPECT) in drug-naïve patients with moderate AD.

Materials and Methods

Study design

This study was conducted between April 2015 and December 2016. Drug-naïve patients with moderate AD underwent imaging assessments with 18F-FDG-PET and 99mTc-ECD-SPECT. Each patient then received open-label treatment with memantine for 12 weeks, and the clinical assessments and imaging assessments were repeated after the treatment.

Participants

Twenty participants (6 men and 14 women) who had been diagnosed with Alzheimer's disease (AD) were recruited from the outpatients of Sunagawa City Medical Center

Hospital for Psychiatry, Sunagawa, Japan. The inclusion criteria were: 1) patients who met the clinical diagnosis of AD based on the criteria of both the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) and the National Institute on Aging-Alzheimer's Association (NIA-AA); and 2) patients with baseline MMSE scores of 14 to 19.

Participants were excluded if they had the following: dementia due to other than Alzheimer's disease; evidence of other neurologic or psychiatric disorders; any medication with central nervous system activity; having serious health problems, and abnormal results of biochemical analysis that may affect cognition. All candidate patients were examined by experienced psychiatrists and received full clinical assessment, which included standard dementia screening with the Mini-Mental State Examination (MMSE), routine blood tests with complete blood count, biochemistry, thyroid function tests, vitamin levels, standard urine analysis. MMSE and Neuropsychiatric Inventory (NPI) assessments were made for each patient on the day they visited for SPECT scans. Informed written consent was obtained from all included participants and their relatives.

This study was carried out according to the Declaration of Helsinki. Each participant's privacy was protected, and the protocol was approved by the Ethics and Radiation

119 Safety Committees of Sunagawa City Hospital, Sunagawa, Japan.

120

121 Memantine treatment

122 On the day following 18F-FDG-PET imaging, patients started taking open-label

123 memantine 5 mg once daily. The dosage was increased over 4 weeks, rising 5 mg per

124 week to a final dosage of 20 mg once daily.

125

126 Clinical assessments

127 Each participant's dementia symptoms were assessed using the MMSE and NPI. The

128 MMSE was included as an overall measure of cognitive impairment. The NPI assesses

129 behavioral and psychological disturbances occurring in patients with dementia. Both the

130 severity and frequency of each symptom were measured, and this information was

131 obtained from a caregiver familiar with the patient [22].

132

133 18F-FDG-PET imaging

134 PET imaging of cerebral metabolic activity in the resting state was performed using a

135 Discovery PET/CT 600 scanner (GE Health care, Milwaukee, WI, USA). Each

136 participant received an intravenous injection of 169.5–325.6 MBq 18F-FDG purchased

137 from Nihon Medi-Physics Co., Ltd. Participants rested quietly in a dimly-lit room
138 during the 40-minute uptake phase. They were then positioned symmetrically dorsally
139 in the scanner. For the acquisition of PET imaging, a 15-minute emission scan in
140 list-mode was performed after the CT scan for attenuation correction. PET images were
141 reconstructed with 3D ordered subset expectation maximization (VUE Point HD).
142
143 99mTc- ECD-SPECT imaging
144 Each participant received a 444.0–1085.0 MBq intravenous injection of 99mTc-ECD as
145 a commercially supplied kit (Neurolite® injection Daiichi; Fujifilm RI Pharma, Japan)
146 while lying down with their eyes closed in a quiet room. Nine minutes after the
147 injection of 99mTc-ECD, brain SPECT was performed for 20 minutes using an E.CAM
148 Signature Series scanner (Toshiba Medical Systems Corporation, Tokyo, Japan)
149 equipped with a low energy high resolution collimator. Projection data were obtained in
150 continuous mode, for 90 steps of 360° at 4° per step. The scanned data were prefiltered
151 with a Butterworth filter (order 8 and a cut off at 0.11 cycles/ pixel). Brain images were
152 reconstructed with filtered back projection. Attenuation correction was performed using
153 Chang's method.
154

155 Imaging and Data analyses

156 PET and SPECT data were analyzed using PMOD 3.5 software (PMOD Technologies,
157 LLC, Switzerland) and statistical parametric mapping 8 (SPM8; Wellcome Trust
158 Centre for Neuroimaging) in Matlab 8 (MathWorks, Inc. Natick, MA, USA). Initially,
159 all imaging data after the reconstruction was re-positioned, and then cortical metabolic
160 activities were corrected by the standardized uptake value (SUV) of 18F-FDG using
161 PMOD. PET images were normalized to Montreal Neurological Institute (MNI) atlas
162 space using the PET template in SPM8 and smoothed using an 8 mm Gaussian filter.
163 SPECT data were also normalized to MNI atlas space using the SPECT template in
164 SPM8 smoothed with an 8 mm Gaussian filter. The global mean uptake in the entire
165 brain was estimated by region-of-interest analysis referring to the Automated
166 Anatomical Labeling (AAL) atlas, and then the SPECT brain perfusion pattern was
167 evaluated by the whole brain uptake ratio (WBR). PET and SPECT images in the
168 baseline condition (pre-memantine treatment) were compared with the post-treatment
169 condition (after 12 weeks of memantine treatment) using the paired t test procedure in
170 SPM8, with $p < 0.01$ for PET and SPECT at the voxel level, respectively. In addition
171 to the SPM analysis, volume of interest (VOI) analysis was performed utilizing VOIs
172 defined in the PMOD AAL atlas. Each PET (SUV) and SPECT (WBR) value of each

173 VOI was obtained from normalized images. SUV and WBR values between baseline
174 and post treatment were compared using paired t-tests.
175
176 Statistical analysis
177 Statistical analyses were performed with the R Statistical Software Package version
178 3.1.0 (R Core Team. Foundation for Statistical Computing, Vienna, Austria).
179 Descriptive statistics and frequency distributions of baseline demographics and
180 cognitive scores were summarized. Data from clinical assessments were analyzed using
181 paired t-tests for comparison between baseline and after 12 weeks of memantine
182 treatment. Statistical significance was set at $p < 0.01$.
183
184 **Results**
185 Patient Characteristics
186 Of the 20 patients enrolled three were excluded from the analysis: One patient was not
187 administrated with memantine at first visit, one lacked second scan data due to health
188 reasons not related to memantine administration, and the third was revealed to have
189 Lewy body dementia. The other 17 patients consisted of 6 men and 11 women, with an
190 average age of 80.1 (6.2) years old. At baseline the mean (standard deviation [SD])

onset age was 78.3 (6.7) years old, mean education 9.5 (1.2) years, and the average body weight 55.3 (13.5) kg. The average MMSE was 16.6 (1.8) at baseline and 16.9 (4.1) post-treatment. The average NPI score was 2.8 (7.6) at baseline and 3.9 (9.2) post-treatment. The patient characteristics are shown in Table 1.

Changes in brain metabolic activity

Brain regions showing significant increases in brain metabolism are highlighted in Figure 1. Significant increases in metabolic activity were observed in wide range of whole cerebral cortical areas. VOIs showing significant increases in SUV were observed in the right inferior parietal lobule, right supramarginal gyrus, right angular gyrus, and right paracentral lobule (Table 2).

Changes in cerebral blood flow

Brain regions with significant increases in cerebral blood flow are shown in Figure 2. Although a wide range of whole cerebral cortexes showed significant increases in brain metabolism (Figure 1), the brain regions in which significant increases in cerebral blood flow occurred were quite limited. No regions had VOIs with significant increases in WBR.

209

210 **Discussion**

211 This study shows, for the first time, a significant increase in brain metabolic activity in
212 wide range of whole cerebral cortexes in drug-naïve AD patients after 12-weeks of
213 memantine treatment alone. Additionally, we revealed that only a limited number of
214 brain regions showed significant increases in cerebral blood flow after 12 weeks of sole
215 memantine treatment in the same previously drug-naïve AD patients.
216 The regions of metabolic increases in this study were wider than those seen in the
217 previous study by Sultzer *et al.* [21]. We speculate that the difference in the ranges of
218 the two studies might be due to the different study designs. While we administered
219 memantine to drug-naïve AD patients, Sultzer *et al.* added memantine treatment to
220 patients on stable ChEI medication, and so the effect of memantine alone could not be
221 assessed in their study. Actually, increased brain metabolism in left prefrontal cortex
222 was demonstrated in a previous study of ChEI treatment [23]. Conversely, the metabolic
223 increases in the angular and supramarginal gyri observed in our study were consistent
224 with that observed by Sultzer *et al.* [21]. We speculate that the increased metabolic
225 activity in these regions was due to memantine.
226 This is the first study to investigate the same drug-naïve AD patients before and after

memantine treatment using 18F-FDG-PET and 99mTc-ECD-SPECT. We found that the regions with increased activity on 18F-FDG-PET and 99mTc-ECD-SPECT were not consistent. This suggests that the increase in brain metabolism following memantine treatment is not directly caused by an increase in regional blood flow.

The targets of memantine, NMDARs, are one of the key players in pathophysiology of AD [24,25]. There are two types of NMDARs, synaptic NMDARs (sNMDARs) and extrasynaptic NMDARs (eNMDARs). It is believed that eNMDARs are linked to cell death signaling, and that sNMDARs are associated with cell survival signal [26,27]. In AD patients, Aβ accumulation sequentially induces astrocytic glutamate release, increases of eNMDAR activity, and synaptic loss due to eNMDAR-mediated excitotoxicity [26,28-31]. Furthermore, eNMDAR activation impairs long-term potentiation through excessive Ca^{+} influx, which also impairs neuronal plasticity [32,33]. The loss of synapses and the impairment of neuronal plasticity induced by eNMDAR activation are most likely the causes of learning and memory impairment [24,26].

The therapeutic mechanisms of memantine could involve preferentially blocking eNMDAR activation [34] and its downstream signaling, enhancing neuronal survival and synaptic plasticity, and suppressing the impairment of long term potentiation in

245 brains of AD patients. We hypothesize that enhancement of neuronal survival and
246 synaptic plasticity, and normalization of long term potentiation caused by blockage of
247 eNMDAR, might increase brain metabolism before cerebral blood flow is increased by
248 synaptic dysfunction recovery.
249 Chen *et al.* reported that the potentiation of brain-derived neurotrophic factor (BDNF)
250 levels in serum and brain are observed in rats treated with low-dose memantine [35].
251 BDNF plays crucial roles in neuronal survival, neurotransmitter modulation, and leads
252 to neuronal plasticity throughout its tyrosine kinase receptors B [36,37]. In addition,
253 BDNF shows neuroprotective activity by increasing sNMDAR activity and reducing
254 eNMDAR activity [38]. Such neurotrophic effects of memantine might cause
255 neuroprotection and neuro-regeneration, and inhibit memory impairment in AD patients.
256 There are limitations to our study. As this study was an open-label single arm
257 exploratory study with a small number of patients (n = 17), additional larger scale
258 double-blind, placebo-controlled studies are necessary for further verification of our
259 findings.
260 We believe this is the first study focusing on brain metabolic activity and perfusion in
261 the same moderate AD patients before and after memantine treatment. Our findings
262 suggest that memantine, independently from any increase in blood flow, improves brain

263 metabolism in patients with moderate AD.

264

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269

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273 manuscript.

274

275 **Competing and conflicting interests**

276 The authors declare that they have no competing interests.

277

278 **References**

279 1. Reisberg B, Doody R, Stoffler A, *et al.* Memantine in moderate-to-severe

280 Alzheimer's disease. *N. Engl. J. Med* 348(14), 1333-1341 (2003).

2. Tariot PN, Farlow MR, Grossberg GT, *et al.* Memantine treatment in patients with moderate to severe Alzheimer's disease already receiving donepezil: a randomized trial. *JAMA* 201, 317-324 (2004).

3. Holman BL, Johnson KA, Gerada B, *et al.* The scientigraphic appearance of Alzheimer's disease: a prospective study using technetium-99m-HMPAO SPECT. *J. Nucl. Med* 33, 181-185 (1992).

4. Bartenstein P, Minoshima S, Hirsch C, *et al.* Quantitative assessment of cerebral blood flow in patients with Alzheimer's disease by SPECT. *J. Nucl. Med* 38(7), 1095-1101 (1997).

5. Bonte FJ, Weiner MF, Bigio EH, *et al.* SPECT imaging in dementias. *J. Nucl. Med* 42(7), 1131-1133 (2001).

6. Pagani M, Salmaso D, Ramstrom C, *et al.* Mapping pathological 99mTc-d, I-Hexamethylpropylene amine oxime uptake in Alzheimer's disease and frontal lobe dementia with SPECT. *Dement. Geriatr. Cogn. Disord* 12: 177-184 (2001).

7. Johnson KA, Holman BL, Mueller SP, *et al.* Single photon emission computed tomography in Alzheimer's disease. Abnormal iofetamine I 123 uptake reflects dementia severity. *Arch. Neurol* 45(4), 392-396 (1988).

298 8. Duara R, Grady C, Haxby J, Sundaram M, *et al.* Positron emission tomography in
299 Alzheimer's disease. *Neurology* 36(7), 879-887 (1986).
300 9. Herholz K, Carter SF, Jones M. Positron emission tomography imaging in dementia.
301 *Br. J. Radiol* 80, S160-S167 (2007).
302 10. Engler H, Forsberg A, Almkcst O, *et al.* Two-year follow-up of amyloid deposition
303 in patients with Alzheimer's disease. *Brain* 129, 2856-2866 (2006).
304 11. Hirono N, Hashimoto M, Ishii K, *et al.* One-year change in cerebral glucose
305 metabolism in patients with Alzheimer's disease. *Am. J. Psychiatry Clin. Neurosci*
306 16, 488-492 (2004).
307 12. Alexander G, Chen K, Pietrini P, *et al.* Longitudinal PET Evaluation of cerebral
308 metabolic decline in Dementia: A potential Outcome measure in Alzheimer's
309 disease treatment studies. *Am. J. Psychiatry* 159, 738-745 (2002).
310 13. Stefanova E, Wall A, Almkvist O, *et al.* Longitudinal PET evaluation of cerebral
311 glucose metabolism in rivastigmine treated patients with mild Alzheimer's disease.
312 *J. Neural. Transm* 113(2), 205-218 (2006).
313 14. Ito K, Shimano Y, Imabayashi E, *et al.* Concordance between (99m)Tc-ECD
314 SPECT and 18F-FDG PET interpretations in patients with cognitive disorders
315 diagnosed according to NIA-AA criteria. *Int. J. Geriatric Psychiatry* 29(10),

316 1079-1086 (2014).

317 15. Shimizu S, Kaneta H, Hirose D, *et al.* Differential effects of acetylcholinesterase
318 inhibitors on clinical responses and cerebral blood flow changes in patients with
319 Alzheimer's disease: A 12-month, randomized, and open-label trial. *Dement.*
320 *Geriatr. Cogn. Disord. Extra* 5, 135-146 (2015).

321 16. Cerci S, Tamam Y, Kaya H, *et al.* Effect of Rivastigmine on regional cerebral blood
322 flow in Alzheimer's disease. *Advances in Therapy* 24(3), 611-621 (2007).

323 17. Ceravolo R, Volterrani D, Tognoni G, *et al.* Cerebral perfusional effects of
324 cholinesterase inhibitors in Alzheimer's disease. *Clin. Neuropharmacol* 27(4),
325 166-170 (2004).

326 18. Nakano S, Asada T, Matsuda H, *et al.* Donepezil hydrochloride preserves regional
327 cerebral blood flow in patients with Alzheimer's disease. *J. Nucl. Med* 42(10),
328 1441-1445 (2001).

329 19. Nobili F, Koulibaly M, Vitali P, *et al.* Brain perfusion follow-up in Alzheimer's
330 patients during treatment with acetylcholinesterase inhibitors. *J. Nucl. Med* 43(8),
331 983-990 (2002).

332 20. Keller C, Kadir A, Forsberg A, *et al.* Long-term effects of galantamine treatment on
333 brain functional activities as measured by PET in Alzheimer's disease patients. *J.*

Alzheimer's Disease 24, 109-123 (2011).

21. Sultzer D, Melrose R, Harwood D, *et al.* Effect of memantine treatment on regional cortical metabolism in Alzheimer's disease. *Am. J. Geriatr. Psychiatry* 18, 606-614 (2010).

22. Cummings JL, Mega M, Gray K, *et al.* The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44(12), 2308-2314 (1994).

23. Teipel SJ, Drzezga A, Bartenstein P, *et al.* Effects of donepezil on cortical metabolic response to activation during (18)FDG-PET in Alzheimer's disease: a double-blind cross-over trial. *Psychopharmacology* 187(1), 86-94 (2006).

24. Zhang Y, Li P, Feng J, *et al.* Dysfunction of NMDA receptors in Alzheimer's disease. *Neurol. Sci* 37(7), 1039-47 (2016).

25. Banding H. Therapeutic targeting of the pathological triad of extrasynaptic NMDA receptor signaling in neurodegenerations. *J. Exp. Med* 214(3) 569-578 (2017).

26. Parsons MP, Raymond LA. Extrasynaptic NMDA receptor involvement in central nervous system disorders. *Neuron* 82, 279-293 (2014).

27. Huang Y, Shen W, Su J, *et al.* Modulating the balance of synaptic and extrasynaptic NDMA receptors shows positive effects against amyloid-β-induced neurotoxicity. *J. Alzheimer's Dis* 57(3), 885-897 (2017).

28. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297(5580), 353-356 (2002).

29. Parameshwaran K, Dhanasekaran M, Suppiramaniam V. Amyloid beta peptides and glutamatergic synaptic dysregulation. *Exp. Neurol* 210(1), 7-13 (2008).

30. Jack CR Jr, Knopman DS, Jagust WJ, *et al.* Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 9(1), 119 (2010).

31. Talantova M, Sanz-Blasco S, Zhang X, *et al.* Aβ induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss. *Proc. Natl. Acad. Sci. U S A* 110(27), E2518-2527 (2013).

32. Hanson JE, Pare JF, Deng L, *et al.* Altered GluN2B NMDA receptor function and synaptic plasticity during early pathology in the PS2APP mouse model of Alzheimer's disease. *Neurobiol. Dis* 74, 254-262 (2015).

366 33. Li S, Jin M, Koeglsperger T, *et al.* Soluble Aβ oligomers inhibit long-term
367 potentiation through a mechanism involving excessive activation of extrasynaptic
368 NR2B-containing NMDA receptors. *J. Neurosci* 31(18), 6627-6638 (2011).
369 34. Xia P, Chen HS, Zhang D, *et al.* Memantine preferentially blocks extrasynaptic
370 over synaptic NMDA receptor currents in hippocampal autapses. *J. Neurosci*
371 30(33), 11246-11250 (2010).
372 35. Chen SL, Tao PL, Chu CH, *et al.* Low-dose memantine attenuated morphine
373 addictive behavior through its anti-inflammation and neurotrophic effects in rats. *J.*
374 *Neuroimmune Pharmacol* 7, 444-453 (2001).
375 36. Harward SC, Hedrick NG, Hall CE, *et al.* Autocrine BDNF-TrkB signalling within
376 a single dendritic spine. *Nature* 538(7623), 99-103 (2016).
377 37. Kocahan S, Doğan Z. Mechanisms of Alzheimer's disease pathogenesis and
378 prevention: the brain, neural pathology, N-methyl-D-aspartate receptors, tau protein
379 and other risk factors. *Clin. Psychopharmacol. Neurosci* 15(1), 1-8 (2017).
380 38. Lau D, Benqtson CP, Buchthal B, *et al.* BDNF reduces toxic extrasynaptic NMDA
381 receptor signaling via synaptic NMDA receptors and nuclear-calcium-induced
382 transcription of inhba/activin A. *Cell Rep* 12(8) 1353-1366 (2015).

383

384 **Figure Legends**

385

386 **Figure 1:** Statistical maps of higher metabolic activity after 12 weeks of memantine
387 treatment compared with baseline.
388 Regions with significantly higher metabolism ($p < 0.01$; paired t-test) superimposed on
389 a standard 3-dimensional anatomic template (3D-render) (A) and co-registered MRI
390 slices (B).

391

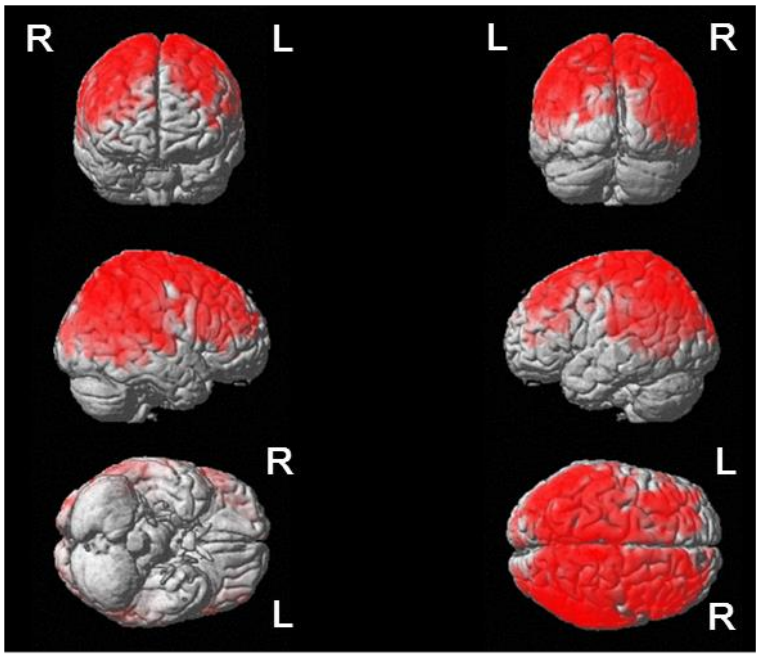
392 **Figure 2:** Statistical maps of higher cerebral blood flow after 12 weeks of memantine
393 treatment compared with baseline.
394 Regions with significantly higher blood flow ($p < 0.01$; paired t-test) superimposed on a
395 standard 3-dimensional anatomic template (3D-render) (A) and co-registered MRI slices
396 (B).

397

398

Figure 1

(A)



(B)

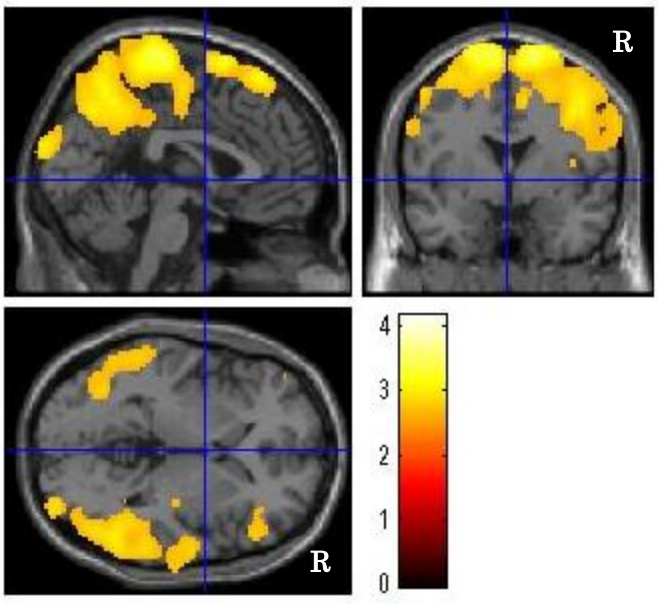
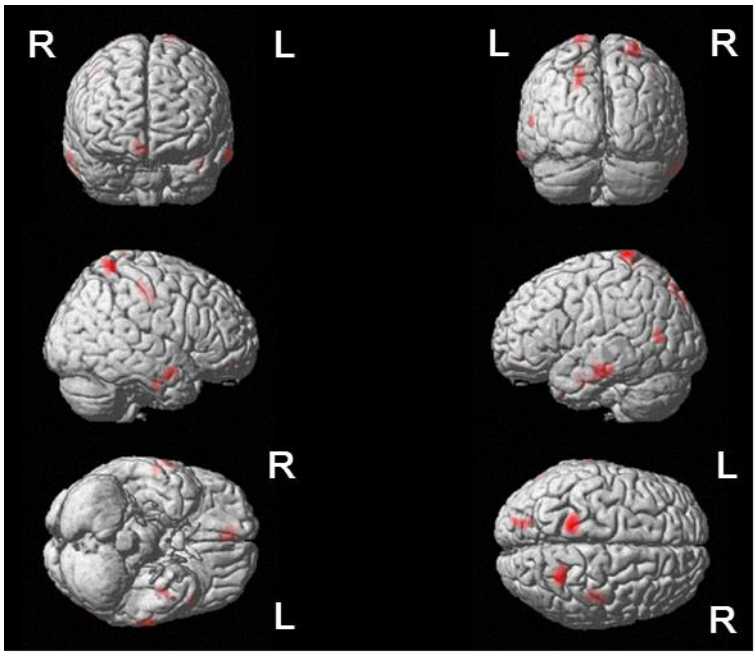


Figure 2

(A)



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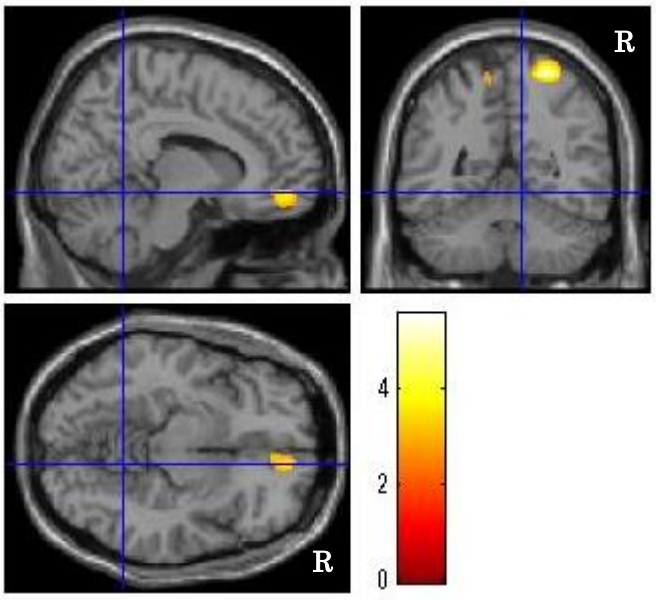

410 **Tables**

411

412 **Table 1:** Baseline demographic characteristics and clinical assessment scores at baseline
413 and after 12 weeks memantine treatment

Characteristics	Baseline (n = 17)	Posttreatment (n = 17)	P value[d)]
Men[a)]	6 (35)		—
Women[a)]	11 (65)		—
Age, mean (SD), y	80.1 (6.2)		—
On set age, mean (SD),y	78.3(6.7)		
Education, mean (SD), y	9.5 (1.2)		—
Weight, mean (SD), kg	55.3 (13.5)		—
MMSE score[b)], mean (SD)	16.6 (1.8)	16.9 (4.1)	0.75
NPI score[c)], mean (SD)	2.8 (7.6)	3.9 (9.2)	0.11

414 Abbreviations: MMSE, Mini-mental State Examination; NPI, Neuropsychiatric
415 Inventory.
416 a) Data are No. (%).
417 b) Lower score reflects greater cognitive impairment
418 c) Lower score reflects fewer behavioral and psychological symptoms.
419 d) Paired t test, post-treatment versus baseline (df = 16).

420

421 **Table 2.** VOIs showing significant increases ($p < 0.01$) in SUV or WBR after 12 weeks
422 of memantine treatment.

VOI	FDG-PET(SUV)			ECD-SPECT(WBR)		
	baseline	post-treatment	P value[a)]	baseline	post-treatment	P value[a)]
Inf_Parietal_r	6.07	7.04	0.009	0.98	0.98	0.952
Supra_Marginal_r	5.99	6.84	0.009	1.05	1.06	0.445
Angular_r	6.07	7.02	0.009	0.97	1.00	0.035
Paracentral_Lobule_r	5.97	6.84	0.006	1.07	1.06	0.305

423 Abbreviations: SUV, standardized uptake value; WBR, whole brain ratio; Inf_Parietal_r,
424 right inferior parietal lobule; Supra_Marginal_r, right supramarginal gyrus; Angular_r,
425 right angular gyrus; Paracentral_Lobule_r, right paracentral lobule; VOI, volume of
426 interest.
427 a) Paired t test, post-treatment versus baseline (df = 16).