Title

Combined treatment with escitalopram and memantine increases gray matter volume and cortical thickness compared to escitalopram and placebo in a pilot study of geriatric depression.

Authors

Krause-Sorio, Beatrix
Siddarth, Prabha
Kilpatrick, Lisa
et al.

Publication Date

2020-09-01

DOI

10.1016/j.jad.2020.05.092

Peer reviewed

HHS Public Access

Author manuscript

J Affect Disord. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

J Affect Disord. 2020 September 01; 274: 464–470. doi:10.1016/j.jad.2020.05.092.

Combined treatment with escitalopram and memantine increases gray matter volume and cortical thickness compared to escitalopram and placebo in a pilot study of geriatric depression.

Beatrix Krause-Sorio[1], **Prabha Siddarth**[1], **Lisa Kilpatrick**[1], **Kelsey T. Laird**[1], **Michaela M. Milillo**[1], **Linda Ercoli**[1], **Katherine L. Narr**[2], **Helen Lavretsky**[1]

[1]Jane and Terry Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, CA, 90095, USA

[2]Department of Neurology, 635 Charles E. Young Drive South, Los Angeles, CA, 90095, USA

Abstract

Background: Geriatric depression with subjective cognitive complaints increases the risk of Alzheimer's Disease (AD). Memantine is a cognitive enhancer used to treat AD. In a 6-month double-blind randomized placebo-controlled trial of escitalopram and memantine (ESC/MEM), ESC/MEM improved cognition at 12 month in geriatric depression (NCT01902004). We now investigated structural neuroplastic changes at 3 months.

Methods: Forty-one older depressed adults (mean age=70.43, SD=7.33, 26 female) were randomized to receive ESC/MEM or ESC/PBO. Mood scores (Hamilton Depression Rating Scale, HAMD) and high-resolution structural T1-weighted images were acquired at baseline and 3 months. Freesurfer 6.0 for image processing and General Linear Models was used to examine group differences in symmetrized percent change gray matter volume (GMV) and cortical thickness, controlling for age and intracranial volume. Nonparametric tests were used to investigate group differences in mood and subcortical volume change.

Results: Among 27 completers (ESC/MEM n=13; ESC/PBO n=14), 62% achieved remission (HAMD≤6) with ESC/MEM and 43% with ESC/PBO (Fisher's exact p=.45). Change in HAMD did not differ between groups (F(1,23)=.14, p=.7). GMV and thickness increased more with

Corresponding author: Helen Lavretsky, Professor of Psychiatry in Residence, Director, Late-Life Mood, Stress, and Wellness Research Program, Jane and Terry Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine at University of California, Los Angeles (UCLA), 760 Westwood Plaza, Los Angeles, CA 90095, Phone: (310) 794-4619, Fax: (310) 206-4399, hlavretsky@mednet.ucla.edu.

Author contributions

H.L. conceived the study. H.L., P.S., L.E. and K.N. designed the study. B.K.S., P.S. and L.K. designed and executed the analysis. K.L. and M.M. contributed to the completion of the study and advised on the manuscript. B.K.S., H.L. and P.S. wrote the article.

Conflict of interest

Dr Lavretsky has received research grants from Allergan, NIMH, NCCIH, PCORI and the Alzheimer's Research & Prevention Foundation. The other authors report no conflicts of interest.

ESC/MEM than with ESC/PBO in the left middle and inferior temporal lobe, right medial, and lateral orbito-frontal cortex (OFC).

Limitations—included small sample size, dropout, and the lack of cognitive data at 3 months.

Conclusions: Although significant group differences in mood improvement were not observed, ESC/MEM resulted in increased GMV and cortical thickness in several brain regions compared to placebo. Larger longitudinal clinical trials can further examine the neuroprotective effect of memantine in geriatric depression.

Introduction

Geriatric depression affects between 10-15% of individuals aged 60 years and older (Ismail et al., 2013). This debilitating condition presents with reduced remission rates as well as cognitive impairment, including subjective memory complaints and memory decline, and executive dysfunction that often precedes dementia (Diniz et al., 2013; Mitchell and Subramaniam, 2005; Singh-Manoux et al., 2017; Wilkins et al., 2009). Cognitive impairment is also associated with increased risk of injuries, falls, and subsequent hospitalization, as well as poor daily functioning and treatment prognosis (Carpenter et al., 2014; Mansbach and Mace, 2018; Tunvirachaisakul et al., 2018). These risks underscore the importance of early diagnosis and treatment of cognitive symptoms in older adults with depression.

Mild cognitive impairment (MCI) is characterized by cognitive decline and associated with gray matter atrophy. Atrophy typically begins in the medial temporal lobe (MTL), which contain brain regions involved in memory (the hippocampus) and emotion regulation (the amygdala), as well as in prefrontal regions involved in executive functions (Nickl-Jockschat et al., 2012). Similar patterns of atrophy (of the amygdala, hippocampus, medial frontal cortex, and orbito-frontal cortex (OFC)) have been observed in geriatric depression (Ballmaier et al., 2004; Du et al., 2014; Lavretsky et al 2007; Sexton et al., 2013). Biomarkers of geriatric depression and amnestic mild cognitive impairment (aMCI) also include atrophy in the inferior frontal gyrus bordering the insula and the medial frontal gyrus (Xie et al., 2012).

Only few studies have investigated treatment-related structural brain changes in geriatric depression. Greater improvement in depressive symptom severity was associated with increases in GMV in frontal regions after three months of treatment with venlafaxine (Droppa et al., 2017), suggesting that antidepressant treatment may restore reduced cortical volume in regions relevant for depressive symptoms. In a small sample, we recently observed reductions in cortical thickness after three months of treatment with levomilnacipran compared to placebo in geriatric depression (Krause-Sorio et al., 2019). In a cross-sectional study, we reported that orbito-frontal GMV in elderly depressed subjects with a history of antidepressant use was higher than in drug-naïve participants, suggesting that antidepressant treatment may have long-term protective effects on brain structure (Lavretsky et al., 2005).

The treatment response to the first-line antidepressants in older adults remains limited, with roughly 70% of depressed older adults responding to a selective serotonin reuptake inhibitor (SSRI) after 8-12 weeks of treatment (Chen et al., 2011) and only 30-40% achieving remission (Nelson et al., 2008). Memantine is a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist that is currently FDA-approved for the treatment of cognitive symptoms in dementia (McShane et al., 2006). In the parent study, we examined the efficacy of the combination ESC/MEM in a double-blind, randomized placebo-controlled trial of geriatric major depression with subjective memory complaints (Lavretsky et al 2019; [NCT01902004]). In the current report, we investigated group differences in whole-brain GMV change between ESC/MEM and ESC/PBO following three months of treatment in a subset of these participants from the parent trial.

Methods

Participants

Forty-one older adults diagnosed with major depressive disorder (MDD, >60 years, mean age=70.5, SD=7.4; 16 male/26 female) who participated in a randomized clinical trial (RCT-NCT01902004) comparing ESC/MEM vs. ESC/PBO underwent an MRI scan at baseline (for patient characteristics, see Table 1). One participant dropped out prior to randomization. The resulting groups consisted of 23 participants in the ESC/MEM and 18 in the ESC/PBO group. The follow up assessments with an MRI scan were performed at three months.

Eligibility criteria were defined as follows: 1) 60 years or older; 2) a diagnosis of MDD according to the Diagnostic and Statistical Manual (DSM-5) diagnostic criteria (American Psychiatric Association, 2013) and a Hamilton Rating Scale for Depression (HAMD; Hamilton, 1967; score >=16; 3) a Mini-Mental State Examination (MMSE; Folstein et al., 1975; score >=23; and 4) subjectively reported memory impairment. Exclusion criteria involved 1) a prior history of psychiatric disorders, such as substance abuse disorder, suicidal behavior or recent suicide attempts in the past year; 2) acute, severe or recent medical illness; 3) a history of allergies or intolerance to either escitalopram or memantine. Seventy-eight percent of participants in our study suffered from chronic depression at baseline (i.e., an episode lasting longer than 24 months) with multiple prior antidepressant trials. However, participants were drug free for at least two weeks prior to randomization, and at least four weeks, if they were taking fluoxetine. None of the participants took cognitive enhancers at study entry. The study was approved by the Institutional Review Board (IRB) at UCLA. Participants signed written informed consent prior to the beginning of the assessment procedure.

Clinical measures

Depressive symptom severity at baseline and three month follow up was assessed using the HAMD representing the primary outcome variable in the clinical study (Hamilton, 1967; Lavretsky et al., 2019). Remission was defined as having a HAMD score of six or lower at three months.

Cognitive assessment

As a part of diagnostic cognitive evaluation, participants completed the Clinical Dementia Rating Scale (CDR; Hughes et al., 1982), the MMSE (Folstein et al., 1975), the Wechsler Memory Scale Third Edition, WMS-III, including the verbal paired associates subtest (Total or Delayed scores; Wechsler, 1997) and the Hopkins Verbal Learning Test (HVLT; Brandt, 1991).

Assessment of mild cognitive impairment (MCI)

MCI was defined as: 1) the stage between normal cognition and dementia; i.e. a CDR score of 0.5; 2) subjective report of cognitive decline as experienced by the patient or a collateral; 3) the absence of significant functional impairment, and 4) objective neurocognitive impairment. Objective neurocognitive impairment was defined as scores of at least one standard deviation (SD) below age- and education-specific norms on at least two screening memory tests: HVLT Total or Delayed scores, and Wechsler Memory Scale Third Edition, WMS-III, verbal paired associates (Total or Delayed scores). Although all participants endorsed subjective memory complaints, only a subset met criteria for MCI. Specifically, participants categorized as having MCI met criteria for aMCI, either single or multiple domains (Winblad et al., 2004).

Medication administration and adherence

The daily dose of escitalopram was 10 mg for the first four weeks of administration. The memantine or matched placebo dose were gradually increased from 5 mg to 20 mg per day over the course of four weeks. The Clinical Global Impression Scale (CGI; Guy, 2000) was administered at baseline and three months as a measure of the overall severity and improvement of depression. Escitalopram doses were increased to 20 mg after four weeks, if the CGI score was >=3. Daily study drug doses were adjusted to a minimum of 5 mg for memantine and 10 mg of escitalopram based on tolerability.

Neuroimaging protocol

A high-resolution T1-weighted MRI image was collected for each participant using either a 3T Siemens TIM Trio or Prisma system (Siemens, Erlangen, Germany) using a 32-channel head coil at the UCLA Ahmanson & Lovelace Brain Mapping Center (ALBMC). Imaging parameters were matched across scanners: a multi-echo MPRAGE scan $1mm^3$ with isotropic voxel dimensions, 176 slices, TR=2,150 ms, TE=1.74, 3.6, 5.46 and 7.32 ms, TI=1,260, FOV=256mm, matrix size=256x256mm, and a flip angle=7 degrees, and all baseline and follow-up scans from each participant were collected on the same MRI system. We used Freesurfer version 6.0 (http://surfer.nmr.mgh.harvard.edu/) for automatic cortical reconstruction. Preprocessing steps and cortical reconstruction included correction of magnetic field inhomogeneities, extraction of brain volume from surrounding tissues, and finally segmentation of subcortical gray matter from white matter and cerebrospinal fluid (CSF) and parcellation of the cortical surface according to the Desikan-Killany atlas (Desikan et al., 2006). Subsequently, we used the automated longitudinal reconstruction pipeline to construct subject-specific templates and register baseline and post-treatment

tissue volumes to each individual template (Reuter et al., 2012). Each resulting scan was carefully inspected for tissue misclassifications and misalignment between baseline and post-treatment scan, and were manually corrected. Smoothing of cortical maps was performed using a Gaussian kernel of 10 mm full-width half-maximum. Subcortical volumes for each hemisphere were extracted for further analysis using statistical software (see Statistics). Subcortical volumes were included for a secondary exploratory analysis (hippocampus, thalamus, caudate, putamen, pallidum and the cerebellum).

Statistics

For the 3-month analysis on change in GMV, we applied a longitudinal volume-based two-stage voxel-wise whole-brain general linear model for each hemisphere using qdec (www.surfer.nmr.mgh.harvard.edu). The model compared between-group differences in GMV symmetrized percent change (SPC), the change rate with respect to the average GMV [i.e. 100 * (annualized rate between time point 1 and time point 2)/average]. This measure does not require a specific order for two time points to be entered; the sign is positive when time point 1 is entered first and negative if time point 2 is entered first (Reuter and Fischl, 2011). SPC further takes into account between-subject variation in inter-time point intervals. Age and total intracranial volume served as covariates in the model. The voxel threshold and Monte-Carlo corrected cluster thresholds for all whole-brain analyses were set to $p<0.05$.

Due to the small sample size, non-parametric methods were used for analyses of subcortical regions. Group differences in change in depression severity (HAMD) and subcortical volumes were examined using rank-based general linear models (GLMs), with treatment group (ESC/MEM vs. ESC/PBO) as the predictor, controlling for the respective baseline HAMD score and age. Subcortical regions examined included left and right hippocampus, thalamus, caudate, putamen, pallidum and the cerebellum. Results for subcortical volumes were corrected for multiple comparisons (adjusted p=.05/12=.004).

Results

Baseline

Baseline demographics, as well as clinical scores and symptoms for each treatment group are detailed in Table 1.

Treatment effects

Of the 41 participants who underwent MRI at baseline, 27 (13 in the ESC/MEM group and 14 in the ESC/PBO group) completed the study. There was no significant difference in remission rates between groups at the end of three months (Fisher's exact p=.45). Remission was achieved by 8/13 completers (61.5%) in the ESC/MEM group, and 6/14 completers (42.9%) in the ESC/PBO group. There was also no significant difference between groups on the change in HAMD ($F(1,23) = .14$, $p = .7$). Increases in GMV and cortical thickness were significantly greater in the ESC/MEM compared to the ESC/PBO group in the left inferior-to-middle temporal lobe and the right medial OFC. In addition, there was a small cluster with increased GMV for memantine compared to placebo in the lateral OFC by the frontal

pole (Figure 2, Table 2). However, no significant changes in subcortical volumes were found between or within groups (Table 3).

Discussion

This pilot study is the first to investigate the treatment effect of the combined SSRI (escitalopram) and memantine on brain morphometry in a 3-month double-blind placebo-controlled RCT in geriatric depression. Similar to results from the parent trial, in this subset of participants who underwent MRI scanning, mood symptoms improved in both treatment groups (Lavretsky et al., 2019). However, increases in both GMV and cortical thickness were specific to the ESC/MEM group compared to ESC/PBO in a large cluster across the left middle to inferior temporal cortex and the right medial OFC. An additional smaller cluster of increased GMV was also found in the right lateral OFC near the frontal pole. The regions found to change with memantine treatment have been reported as reduced in volume in geriatric depression, as well as in MCI and AD (Ballmaier et al., 2004; Du et al., 2014; Lavretsky et al., 2007; Son et al., 2013; Xie et al., 2012). In a mixed sample of geriatric depression, aMCI and a combination of both types, all groups were compared to healthy controls and reduced GMV in the right OFC was specific to depression, while the ventromedial prefrontal cortex was affected in both conditions (Xie et al., 2012). Human studies are supported by rodent models that demonstrated beneficial effects of memantine on stress-induced memory impairment and depressive behavior and increased frontal lobe and hippocampal brain-derived neurotrophic factor (BDNF), a major neuroprotective growth factor with a critical role in synaptic plasticity and neuronal health (Amidfar et al., 2018).

To our knowledge, the effect of memantine on MRI-based measures of neuroplasticity in humans has not been tested. The limited existing evidence on antidepressant-related structural brain changes supports our findings. For example, venlaxafine was found to improve geriatric depression and increase GMV in the frontal lobe after three months of treatment (Droppa et al., 2017). While GMV reductions in the superior orbital frontal gyrus were linked to smaller improvements in depressive symptoms, GMV increases were associated with larger symptom improvement. However, a control group was not available in this study. GMV in the OFC in older adults with depression and a history of antidepressant use was higher than in drug-naïve subjects, which suggests that antidepressant treatment may have long-term neuroprotective effects (Lavretsky et al., 2005). Furthermore, preliminary evidence demonstrates reductions in cortical thickness in right postcentral, supramarginal and lateral occipital cortices and increases in the left insula in geriatric depression after three months of treatment with levomilnacipran compared to placebo (Krause-Sorio et al., 2019).

In younger depressed participants, six months of paroxetine treatment led to increases in GMV in the right middle temporal cortex, whereby larger increases correlated with larger symptom improvement and there was a trend for larger GMV changes in subjects who received higher doses (Lu et al., 2018).

In a limited number of studies reporting intervention-related increases or preservation of cortical structures, other cognitive enhancement techniques including cognitive training,

physical exercise and non-invasive brain stimulation were more successful when used in combination with main therapies for healthy aging, MCI and dementia (Cespon et al., 2018; Engvig et al., 2014; Na et al., 2018; Reiter et al., 2015; Tamura et al., 2015; Zhang et al., 2019). The evidence points to the ability of treatment interventions to enhance gray matter volume and cortical thickness in older adults at risk for AD that can be used to reduce risk for cognitive decline, and the results of this preliminary study add further support for this hypothesis.

The macroscopic mechanisms of our observed GMV and cortical thickness changes are unclear. Rodent models of memantine have observed improved symptoms of depression and memory impairment along with increases in brain-derived neuroptrophic factor (BDNF), especially when administered in combination with antidepressant treatment (Amidfar et al., 2018; Amidfar et al., 2017). Additionally, memantine reduces the formation of amyloid and tau pathology and thereby protects radial glial cells and allows for hippocampal neurogenesis and has the potential to protect against the detrimental effects of excitotoxic effects on brain tissue (Sun et al., 2015; Takahashi-Ito et al., 2017; Trotman et al., 2015; Wang et al., 2015). Further beneficial effects of memantine have been found to include reduced cell atrophy and astrogliosis, increased capillary formation and altered glutamate receptor expression (Wang et al., 2017). While memantine shows positive effects on a variety of molecular mechanisms within the cortex, alternative non-neuronal mechanisms underlying our results could be gliogenesis, synaptogenesis, increases in vasculature or a variety of signaling pathway changes, including BDNF (Zatorre et al., 2012).

The limitations of our study include a relatively small sample size (a relatively large number of clinical trial participants had contraindications to MRI scanning), high dropout, and the absence of a cognitive assessment at three months. However, the presence of cortical changes within three months of treatment suggests that memantine has the potential to induce neuroplastic changes over a relatively short period of time. Future studies should focus on investigating the clinical significance of memantine-induced cortical changes in larger samples.

Acknowledgements

We thank the University of California Los Angeles Ahmanson & Lovelace Brain Mapping Center for their support, particularly the MRI technicians.

Funding

This work was supported by grants R01MH097892, K24AT009198 to Dr. Lavretsky.

References

Amidfar M, Kim YK, Wiborg O, 2018 Effectiveness of memantine on depression-like behavior, memory deficits and brain mRNA levels of BDNF and TrkB in rats subjected to repeated unpredictable stress. Pharmacological Reports 70, 600–606. 10.1016/j.pharep.2017.12.007 [PubMed: 29680698]

Amidfar M, Reus GZ, Quevedo J, Kim YK, Arbabi M, 2017 Effect of co-administration of memantine and sertraline on the antidepressant-like activity and brain-derived neurotrophic factor (BDNF) levels in the rat brain. Brain Res Bull 128, 29–33. 10.1016/j.brainresbull.2016.11.003 [PubMed: 27825855]

Ballmaier M, Kumar A, Thompson PM, Narr KL, Lavretsky H, Estanol L, Deluca H, Toga AW, 2004 Localizing gray matter deficits in late-onset depression using computational cortical pattern matching methods. The American Journal of Psychiatry 161,2091–2099. 10.1176/appi.ajp.161.11.2091 [PubMed: 15514411]

Brandt J, 1991 The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. Clinical Neuropsychologist 5, 125–142. 10.1080/13854049108403297

Carpenter CR, Avidan MS, Wildes T, Stark S, Fowler SA, Lo AX, 2014 Predicting geriatric falls following an episode of emergency department care: a systematic review. Academic Emergency Medicine 21, 1069–1082. 10.1111/acem.12488 [PubMed: 25293956]

Cespon J, Miniussi C, Pellicciari MC, 2018 Interventional programmes to improve cognition during healthy and pathological ageing: Cortical modulations and evidence for brain plasticity. Ageing Research Reviews 43, 81–98. 10.1016/j.arr.2018.03.001 [PubMed: 29522820]

Chen YM, Huang XM, Thompson R, Zhao YB, 2011 Clinical features and efficacy of escitalopram treatment for geriatric depression. The Journal of International Medical Research 39, 1946–1953. 10.1177/147323001103900540 [PubMed: 22117998]

Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ, 2006 An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 31, 968–980. 10.1016/j.neuroimage.2006.01.021 [PubMed: 16530430]

Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd, 2013 Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. The British Journal of Psychiatry 202, 329–335. 10.1192/bjp.bp.112.118307 [PubMed: 23637108]

Droppa K, Karim HT, Tudorascu DL, Karp JF, Reynolds CF 3rd, Aizenstein HJ, Butters MA, 2017 Association between change in brain gray matter volume, cognition, and depression severity: Pre- and post- antidepressant pharmacotherapy for late-life depression. Journal of Psychiatric Research 95, 129–134. 10.1016/j.jpsychires.2017.08.002 [PubMed: 28843842]

Du M, Liu J, Chen Z, Huang X, Li J, Kuang W, Yang Y, Zhang W, Zhou D, Bi F, Kendrick KM, Gong Q, 2014 Brain grey matter volume alterations in late-life depression. Journal of Psychiatry & Neuroscience 39, 397–406 [PubMed: 24949867]

Du X, Mao Y, Ran Q, Zhang Q, Luo Q, Qiu J, 2016 Short-term group cognitive behavior therapy contributes to recovery from mild depression: Evidence from functional and structural MRI. Psychiatry research. Neuroimaging 251, 53–59. 10.1016/j.pscychresns.2016.04.010 [PubMed: 27124424]

Engvig A, Fjell AM, Westlye LT, Skaane NV, Dale AM, Holland D, Due-Tonnessen P, Sundseth O, Walhovd KB, 2014 Effects of cognitive training on gray matter volumes in memory clinic patients with subjective memory impairment. Journal of Alzheimer's Disease 41, 779–791. 10.3233/jad-131889

Folstein MF, Folstein SE, McHugh PR, 1975 "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12, 189–198. 10.1016/0022-3956(75)90026-6 [PubMed: 1202204]

Guy W, 2000 Clinical Global Impressions (CGI) Scale, Modified, In: Rush JA (Ed.), Task Force for the Handbook of Psychiatric Measures. Handbook of Psychiatric Measures 1ed. American Psychiatric Association, Washington, DC.

Hamilton M, 1967 Development of a Rating Scale for Primary Depressive Illness. British Journal of Social and Clinical Psychology 6, 278–296. 10.1111/j.2044-8260.1967.tb00530.x [PubMed: 6080235]

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL, 1982 A new clinical scale for the staging of dementia. The British Journal of Psychiatry 140, 566–572. 10.1192/bjp.140.6.566 [PubMed: 7104545]

Ismail Z, Fischer C, McCall WV, 2013 What characterizes late-life depression? The Psychiatric Clinics of North America 36, 483–496. 10.1016/j.psc.2013.08.010 [PubMed: 24229652]

Krause-Sorio B, Kilpatrick L, Siddarth P, Ercoli L, Laird KT, Aguilar-Faustino Y, Milillo MM, Narr KL, Lavretsky H, 2019 Cortical thickness increases with levomilnacipran treatment in a pilot

randomised double-blind placebo-controlled trial in late-life depression. Psychogeriatrics. 10.1111/psyg.12475

Lavretsky H, Ballmaier M, Pham D, Toga A, Kumar A, 2007 Neuroanatomical characteristics of geriatric apathy and depression: a magnetic resonance imaging study. The American Journal of Geriatric Psychiatry 15, 386–394. 10.1097/JGP.0b013e3180325a16 [PubMed: 17463189]

Lavretsky H, Laird KT, Krause-Sorio B, Heimberg BF, Yeargin J, Grzenda A, Wu P, Thana-Udom K, Ercoli LM, Siddarth P, 2019 A Randomized Double-Blind Placebo-Controlled Trial of Combined Escitalopram and Memantine for Older Adults With Major Depression and Subjective Memory Complaints. The American Journal of Geriatric Psychiatry. 10.1016/j.jagp.2019.08.011

Lavretsky H, Roybal DJ, Ballmaier M, Toga AW, Kumar A, 2005 Antidepressant exposure may protect against decrement in frontal gray matter volumes in geriatric depression. The Journal of Clinical Psychiatry 66, 964–967. 10.4088/jcp.v66n0801 [PubMed: 16086609]

Lu XW, Guo H, Sun JR, Dong QL, Zhao FT, Liao XH, Zhang L, Zhang Y, Li WH, Li ZX, Liu TB, He Y, Xia MR, Li LJ, 2018 A shared effect of paroxetine treatment on gray matter volume in depressive patients with and without childhood maltreatment: A voxel-based morphometry study. CNS Neuroscience & Therapeutics 24, 1073–1083. 10.1111/cns.13055 [PubMed: 30277663]

Mansbach WE, Mace RA, 2018 Predicting Functional Dependence in Mild Cognitive Impairment: Differential Contributions of Memory and Executive Functions. The Gerontologist. 10.1093/geront/gny097

McShane R, Areosa Sastre A, Minakaran N, 2006 Memantine for dementia. The Cochrane Database of Systematic Reviews, Cd003154. 10.1002/14651858.CD003154.pub5

Mitchell AJ, Subramaniam H, 2005 Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. The American Journal of Psychiatry 162, 1588–1601. 10.1176/appi.ajp.162.9.1588 [PubMed: 16135616]

Na HR, Lim JS, Kim WJ, Jang JW, Baek MJ, Kim J, Park YH, Park SY, Kim S, 2018 Multimodal Assessment of Neural Substrates in Computerized Cognitive Training: A Preliminary Study. Journal of Clinical Neurology 14, 454–463. 10.3988/jcn.2018.14.4.454 [PubMed: 30198220]

Nelson JC, Delucchi K, Schneider LS, 2008 Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. The American journal of geriatric psychiatry: official journal of the American Association for Geriatric Psychiatry 16, 558–567. 10.1097/JGP.0b013e3181693288 [PubMed: 18591576]

Nickl-Jockschat T, Kleiman A, Schulz JB, Schneider F, Laird AR, Fox PT, Eickhoff SB, Reetz K, 2012 Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis. Brain Structure & Function 217, 115–125. 10.1007/s00429-011-0333-x [PubMed: 21667303]

Reiter K, Nielson KA, Smith TJ, Weiss LR, Alfini AJ, Smith JC, 2015 Improved Cardiorespiratory Fitness Is Associated with Increased Cortical Thickness in Mild Cognitive Impairment. Journal of the International Neuropsychological Society 21, 757–767. 10.1017/s135561771500079x [PubMed: 26581788]

Reuter M, Fischl B, 2011 Avoiding asymmetry-induced bias in longitudinal image processing. NeuroImage 57, 19–21. 10.1016/j.neuroimage.2011.02.076 [PubMed: 21376812]

Reuter M, Schmansky NJ, Rosas HD, Fischl B, 2012 Within-subject template estimation for unbiased longitudinal image analysis. NeuroImage 61, 1402–1418. 10.1016/j.neuroimage.2012.02.084 [PubMed: 22430496]

Sexton CE, Mackay CE, Ebmeier KP, 2013 A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. The American Journal of Geriatric Psychiatry 21, 184–195. 10.1016/j.jagp.2012.10.019 [PubMed: 23343492]

Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimaki M, Sabia S, 2017 Trajectories of Depressive Symptoms Before Diagnosis of Dementia: A 28-Year Follow-up Study. JAMA Psychiatry 74, 712–718. 10.1001/jamapsychiatry.2017.0660 [PubMed: 28514478]

Son JH, Han DH, Min KJ, Kee BS, 2013 Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. Neuroscience Letters 548, 15–20. 10.1016/j.neulet.2013.05.021 [PubMed: 23727389]

Sun D, Chen J, Bao X, Cai Y, Zhao J, Huang J, Huang W, Fan X, Xu H, 2015 Protection of Radial Glial-Like Cells in the Hippocampus of APP/PS1 Mice: a Novel Mechanism of Memantine in the Treatment of Alzheimer's Disease. Molecular neurobiology 52, 464–477. 10.1007/s12035-014-8875-6 [PubMed: 25195698]

Takahashi-Ito K, Makino M, Okado K, Tomita T, 2017 Memantine inhibits beta-amyloid aggregation and disassembles preformed beta-amyloid aggregates. Biochemical and biophysical research communications 493, 158–163. 10.1016/j.bbrc.2017.09.058 [PubMed: 28917837]

Tamura M, Nemoto K, Kawaguchi A, Kato M, Arai T, Kakuma T, Mizukami K, Matsuda H, Soya H, Asada T, 2015 Long-term mild-intensity exercise regimen preserves prefrontal cortical volume against aging. International Journal of Geriatric Psychiatry 30, 686–694. 10.1002/gps.4205 [PubMed: 25353992]

Trotman M, Vermehren P, Gibson CL, Fern R, 2015 The dichotomy of memantine treatment for ischemic stroke: dose-dependent protective and detrimental effects. J Cereb Blood Flow Metab 35, 230–239. 10.1038/jcbfm.2014.188 [PubMed: 25407270]

Tunvirachaisakul C, Gould RL, Coulson MC, Ward EV, Reynolds G, Gathercole RL, Grocott H, Supasitthumrong T, Tunvirachaisakul A, Kimona K, Howard RJ, 2018 Predictors of treatment outcome in depression in later life: A systematic review and meta-analysis. Journal of Affective Disorders 227, 164–182. 10.1016/j.jad.2017.10.008 [PubMed: 29100149]

Wang X, Blanchard J, Grundke-Iqbal I, Iqbal K, 2015 Memantine Attenuates Alzheimer's Disease-Like Pathology and Cognitive Impairment. PloS one 10, e0145441 10.1371/journal.pone.0145441 [PubMed: 26697860]

Wang YC, Sanchez-Mendoza EH, Doeppner TR, Hermann DM, 2017 Post-acute delivery of memantine promotes post-ischemic neurological recovery, peri-infarct tissue remodeling, and contralesional brain plasticity. J Cereb Blood Flow Metab 37, 980–993. 10.1177/0271678x16648971 [PubMed: 27170698]

Wechsler D, 1997 The Wechsler Adult Intelligence Scale, III Manual. The Psychological Corporation, San Antonio.

Wilkins CH, Mathews J, Sheline YI, 2009 Late life depression with cognitive impairment: evaluation and treatment. Clinical Interventions in Aging 4, 51–57 [PubMed: 19503765]

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC, 2004 Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. Journal of Internal Medicine 256, 240–246. 10.1111/j.1365-2796.2004.01380.x [PubMed: 15324367]

Xie C, Li W, Chen G, Douglas Ward B, Franczak MB, Jones JL, Antuono PG, Li S-J, Goveas JS, 2012 The co-existence of geriatric depression and amnestic mild cognitive impairment detrimentally affect gray matter volumes: Voxel-based morphometry study. Behavioural Brain Research 235, 244–250. [PubMed: 22909988]

Zatorre RJ, Fields RD, Johansen-Berg H, 2012 Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat Neurosci 15, 528–536. 10.1038/nn.3045 [PubMed: 22426254]

Zhang H, Wang Z, Wang J, Lyu X, Wang X, Liu Y, Zeng X, Yuan H, Wang H, Yu X, 2019 Computerized multi-domain cognitive training reduces brain atrophy in patients with amnestic mild cognitive impairment. Translational Psychiatry 9, 48 10.1038/s41398-019-0385-x [PubMed: 30705261]

Highlights

- Geriatric depression with subjective memory complaints increases risk of Alzheimer's disease
- Memantine is a neuroprotective agent that is FDA-approved for treatment of cognitive symptoms in advanced Alzheimer's disease (AD)
- Combination of escitalopram and memantine resulted in increased cortical volume and thickness in brain regions associated with depression and AD compared to escitalopram and placebo
- Neuroprotective effects of memantine in geriatric depression warrant further longitudinal studies

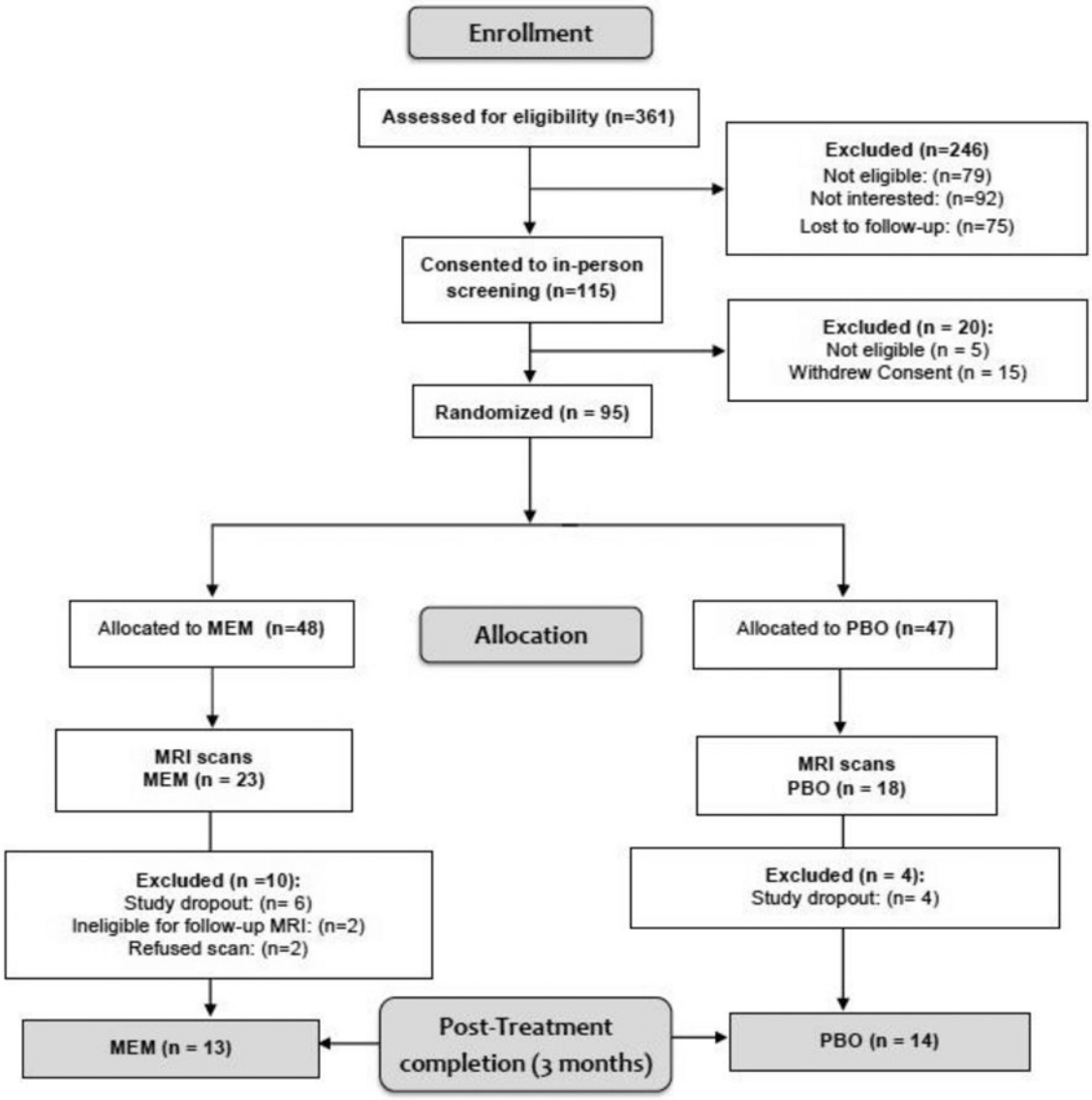

Figure 1.
Consort diagram.

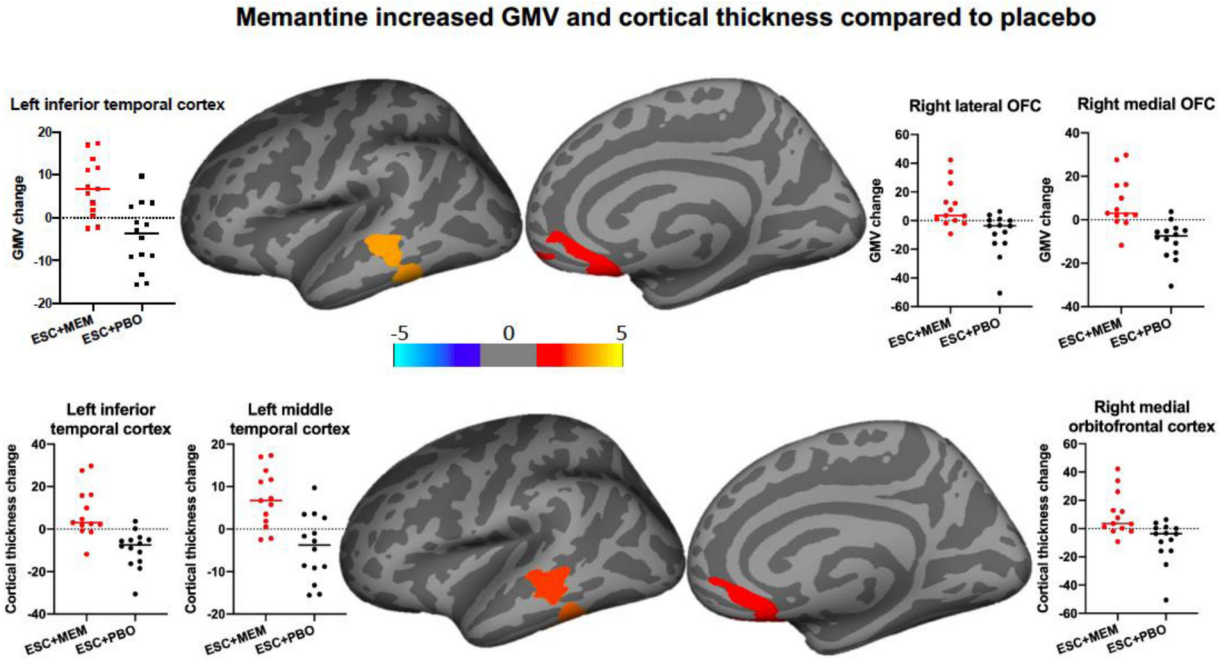

Figure 2. Between-group differences in GMV changes after three months of memantine treatment.

GMV (top panel) and cortical thickness (bottom panel) in the left inferior and middle temporal lobe and the right medial (and for GMV also the lateral OFC) cortices increased significantly more in the memantine compared to the placebo group.

Table 1.

Participant demographics and baseline clinical scores. HAMD = Hamilton Depression Rating Scale; MMSE = Mini Mental State Examination.

Variable	ESC/MEM Median (range) N=13	ESC/PBO Median (range) N=14	Kruskal-Wallis test statistic (p-value)
Age	71 (60-82)	72 (60-83)	.0006 (p=.98)
Education in years	16 (12-18)	16 (13-18)	.09 (p=.76)
HAMD	16 (16-26)	17 (16-23)	.52 (p=.47)
MMSE	29 (28-30)	27.5 (26-30)	2.57 (p=.11)
	N (%)	**N (%)**	**Fisher's exact test**
Male	6 (46.1%)	6 (42.9%)	p=1.0
Female	7 (53.9%)	8 (57.1%)	
MCI	2 (15.4%)	2 (14.3%)	p=1.0

Table 2.

Treatment-related changes in GMV and cortical thickness for each cluster.

Region	Cluster size (mm^2)	MNI coordinates X, Y, Z	Cluster-corrected p-value	Minimum – maximum p
Thickness				
Left hemisphere				
Inferior temporal cortex	741	−49.1, −41.4, −23.2	.0009	.0005-.0013
Middle temporal cortex	676	−53.1, −24.0., −4.0	.0024	.0018-.003
Right hemisphere				
Medial OFC	529	7.1, 22.4, −12.1	.021	.0192-.0228
Gray matter volume (GMV)				
Left hemisphere				
Inferior temporal cortex	1023	−53.1, −24.0, −4.0	.0002	<.00001-.0004
Right hemisphere				
Medial OFC	581	10.8, 14.0, −15.2	.0106	.0093-.0119
Lateral OFC	471	19.9, 51.3, −12.9	.0427	.0401-.0453

Table 3.

Treatment-related changes in subcortical volume.

	ESC/MEM Median GMV change *(min, max)*	ESC/PBO Median GMV change *(min, max)*	Kruskal-Wallis test statistic (p-value)
Subcortical volumes			
Left hemisphere			
Hippocampus	−8.8 *(−182.4, 21.6)*	−32.7 *(−143.8, 18.9)*	.17 (*p*=.68)
Thalamus	−13.6 *(−247.6, 186.3)*	−3.7 *(−285.9, 146.7)*	.13 (*p*=.72)
Caudate	0.3 *(−122.9, 202.5)*	19.9 *(−180.7, 253.4)*	<.01 (*p*=.96)
Putamen	12.3 *(−42.7, 112.2)*	1.2 *(−108.3, 132.3)*	.79 (*p*=.38)
Pallidum	−0.8 *(−111.0, 69.5)*	−3.3 *(−133.0, 109.1)*	.16 (*p*=.69)
Cerebellum	−646.6 *(−2,175.5, 884.1)*	−102.2 *(−1,193.0, 982.5)*	1.82 (*p*=.19)
Right hemisphere			
Hippocampus	−35.8 *(−163.7, 103.7)*	−26.1 *(−225.9, 29.3)*	.14 (*p*=.72)
Thalamus	−33.3 *(−375.6, 88.3)*	−35.4 *(−235.1, 91.3)*	.01 (*p*=.92)
Caudate	−8.7 *(−93.4, 119.5)*	−61.2 *(−301.3, 150.7)*	1.41 (*p*=.25)
Putamen	−17.2 *(−124.3, 117.3)*	−38.3 *(−215.4, 124.8)*	1.63 (*p*=.22)
Pallidum	2.4 *(−76.6, 73.1)*	−21.6 *(−88.1, 95.2)*	.06 (*p*=.82)
Cerebellum	−360.5 *(−2,644.6, 934.2)*	−351.5 *(−1,179.3, 978.9)*	.77 (*p*=.39)