Published in final edited form as:

Psychiatr Clin North Am. 2013 December ; 36(4): . doi:10.1016/j.psc.2013.08.002.

Cognitive Deficits in Geriatric Depression: Clinical Correlates and Implications for Current and Future Treatment

Sarah Shizuko Morimoto^a and George S. Alexopoulos^b

^aAssistant Professor of Psychology in Psychiatry, Institute of Geriatric Psychiatry, Weill Cornell Medical College, White Plains, NY

^bStephen P. Tobin and Dr. Arnold M. Cooper Professor of Psychiatry, Weill Cornell Medical College, White Plains, NY

Synopsis

The purpose of this article is to identify the cognitive deficits commonly associated with geriatric depression, and describe their clinical significance. We then summarize the complex relationship between geriatric depression and dementia and discuss possible shared mechanisms. Last, we present evidence regarding whether the cognitive deficits in depression may be mitigated with medication or with computerized cognitive remediation.

Keywords

Geriatric depression; dementia; cognitive dysfunction; executive function; remission; cognitive remediation

Introduction

Major depression in the elderly is often accompanied by cognitive impairment(1). Although estimates vary, studies have shown that combined depression and cognitive dysfunction is present in roughly 25 per cent of subjects (2). In addition, the number of community residents with both depressive symptoms and impaired cognition doubles every five years after the age of 70. In some cases, the syndromes of depression and cognitive impairment may be related to the same underlying disorders (e.g. vascular dementia, hypothyroidism), whereas in other cases depression and cognitive impairment may have different causes but each may influence the course of the other. Differential diagnosis and treatment decisions

© 2013 Elsevier Inc. All rights reserved.

Corresponding Author: Sarah Shizuko Morimoto, Psy.D., Institute of Geriatric Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Rd., White Plains, NY. 10605, ssm9006@med.cornell.edu.

Co-author: George S. Alexopoulos, M.D. Institute of Geriatric Psychiatry, Weill Cornell Medical College, 21 Bloomingdale Rd., White Plains, NY. 10605, gsalexop@med.cornell.edu

Conflicts of Interest: Dr. Morimoto: None

Dr. Alexopoulos: Consultant: Hoffman-LaRoche, Lilly, Pfizer, Otsuka

Speakers' Bureau: Astra Zeneca, Forest, Novartis, Sunovion

Disclosures: Funding Sources: Dr. Morimoto: NIMH: K 23, MH 095830, Clinical Translational, Science Center.

Dr. Alexopoulos: NIMH: P30, MH085943; R01 MH R01 MH096685; R01 MH075897; R01 MH076829; T32, MH019132; The Sanchez Foundation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

can be complicated for various reasons. Cognitive symptoms of severe depression can be prominent and be misdiagnosed as an early stage dementing disorder. Incipient dementia often has somatic and behavioral symptoms resembling depression. Finally, depression is a common complication of dementing disorders (3). The relationships among cerebrovascular changes, other aging related structural abnormalities, specific forms of cognitive dysfunction, and increased risk for developing dementias in geriatric depression have yet to be reconciled. The varied and most current findings suggest that there are likely multiple pathways to poor cognitive outcomes (4).

Cognitive Deficits in Geriatric Depression

The neuropsychological impairments seen frequently in geriatric depression span across multiple cognitive domains (5). These include impairments in:

- episodic memory (6–8)
- recognition memory
- visuospatial skills(9–11)
- verbal fluency (12)
- psychomotor speed (13, 14)

These impairments, particularly memory impairments, were attributed to dysfunction in subcortical structures related to mood regulation, such as the hippocampus (15).

Recent research has focused on the role of executive functions, such as impaired planning, organizing, initiating, perseverating, sequencing and attention set shifting in the clinical course of geriatric depression (9, 10, 12, 16–18). These studies indicate that abnormal performance on some tests of executive function predicts both poor and unstable antidepressant response (12, 16, 19, 20), as well as current and future disability (21, 22) although some disagreement exists (23). In addition, executive dysfunction has been shown to predict suicidality, even after controlling for comorbid conditions (24, 25). The specifics of this topic are discussed below.

Neurobiological Underpinnings of Cognitive Deficits

The specific structural and functional abnormalities that contribute to the symptoms of depression remain to be uncovered, although several abnormalities have been reported (26). Recently, structural and functional neuroimaging have documented both frontostriatal impairment and a relationship between frontostriatal impairment and executive dysfunction in geriatric depression (27, 28)

Structural abnormalities have been identified in the:

- orbitofrontal cortex (29), particularly the gyrus rectus bilaterally (30, 31)
- anterior cingulate (30, 32)
- caudate head(33)
- putamen(34)
- hippocampus (35, 36)
- amygdala (37)

In addition to grey matter reductions, bilateral white matter hyperintensities are prevalent in geriatric depression (38–41), and mainly occur in the subcortical structures and their frontal

projections (41, 42). White matter hyperintensities disrupt frontostriatal circuits (43) and have been associated with executive dysfunction (10, 27, 38).

Abnormal metabolism has also been noted in limbic regions, including the amygdala (44–46), the pregenual and subgenual anterior cingulate (47), the posterior orbital cortex (48), the posterior cingulate and the medial cerebellum (49). Recent research has shown increased cortical glucose metabolism in both anterior and posterior cortical regions in patients with geriatric depression relative to controls, particularly in areas where there has been cerebral atrophy, which may represent a compensatory response (50). Cortical glucose metabolism was correlated with anxiety and depressive symptoms (50).

Multiple pathways may lead to depression and cognitive impairment. However, clinical as well as structural and functional neuroimaging studies suggest that depressive symptoms and executive impairment originate from related brain dysfunctions (12, 20, 27, 40, 51), at least in a subgroup of elderly patients. We described a ‘depression-executive dysfunction syndrome’ (DED), characterized by symptoms and signs resembling a medial frontal lobe syndrome, including psychomotor retardation, anhedonia, apathy, mild vegetative symptoms and pronounced functional disability disproportional to the severity of the depressive syndrome (5, 16, 52).

Neurocognitive Deficits Influencing Treatment Response of Geriatric Depression

Abnormal performance on select executive function tests was shown to predict poor and/or slow antidepressant response (12, 20, 53–55), a higher level of functional disability (21).

These include processing speed, perseveration, semantic strategy, and response inhibition, which were associated with both poor and unstable antidepressant response and low remission rate in non-demented elderly patients with major depression treated with ‘adequate’ dosages of various antidepressants (8, 12, 16, 18–20, 26, 54–56). However, some disagreement exists (23). Dysfunction in the neural circuits related to remission may produce multiple downstream cognitive abnormalities that are similar (i.e. semantic strategy deficits vs. response inhibition deficits) but not identical, perhaps because of individual differences in network abnormalities, pre-morbid network characteristics and network interactions with other brain systems necessary for completion of tasks(20).

Decrements in performance on the Initiation/Perseveration (I/P) domain of the Dementia Rating Scale (DRS) predict poor response to antidepressant treatment in geriatric depression (19, 57). A meta-analysis examining the relationship between pretreatment cognitive impairment and response to antidepressants demonstrated that only the DRS I/P domain was a reliable predictor of poor antidepressant treatment response(58).

Approximately 42 per cent of elders with major depression have abnormal initiation/perseveration scores as measured by the Mattis Dementia Rating Scale (DRS) (59). Though not a classical test of executive function, the I/P domain of the DRS tests multiple coordinated cognitive skills that require executive functioning. The term ‘executive functions’ encompasses a variety of cognitive abilities, such as planning, organizing, self-monitoring, inhibiting prepotent responses and strategy generation(60, 61). Each of these functions is subserved by distinct, but also shared, neural systems. Furthermore, performance on measures of executive function can affect and be affected by performance in non-executive cognitive domains, such as processing speed, learning, and memory(62).

A recent study, showed that, among the functions tested by the I/P, only the Complex Verbal portion (CV/IP) predicted remission during treatment with escitalopram (12). The CV/IP tests word generation ability by asking patients to name all of the items they can think of in a supermarket (i.e. semantic fluency). Performance on speeded verbal tasks such as the CV/IP can be improved by the use of strategies, such as the organization of responses into super ordinate verbal categories (semantic organization) e.g. replying with words belonging to the same category (fruit) e.g. grapes, strawberries, bananas, oranges, etc. rather than separate categories e.g.: “ bread, bananas, milk, etc. Completing strategic semantic tasks such as the CV/IP also requires selection of words from multiple activated responses, and suppression of semantically or phonemically related but inapplicable words. In the above study, the use of semantic strategy, explained performance differences between remitters and non-remitters(12).

We followed up these findings with a second study that demonstrated that the use of the same executive function; semantic organizational strategy, explained both verbal memory performance and remission rates of geriatric depression (20). These studies are the first to define a single executive function that is predictive of remission with antidepressant drug treatment, regardless of the task by which it is elicited. If these findings are replicated, testing semantic strategy use could be an adjunct to a clinical assessment of depressive symptoms to improve clinician’s ability to identify patients at risk for poor antidepressant drug response (12).

Neurobiological Abnormalities Influencing Treatment Response of Geriatric Depression

Structural neuroimaging has documented frontostriatal abnormalities in late life depression and a relationship of these frontostriatal abnormalities to executive dysfunction (27, 28). A recent study found significant associations between fractional anisotropy in multiple fronto-striato-limbic regions and Stroop Color Word Interference performance, providing evidence for the association of these areas with the executive dysfunction often accompanying geriatric depression (27).

Structural abnormalities in neural systems related to executive functions may be associated with poor remission rate of late-life depression. A recent diffusion tensor imaging (DTI) study suggest that reduced white matter integrity in various fronto-limbic regions (63) (40, 57, 64) predicts failure to remit with antidepressant treatment in geriatric depression. Older patients with major depression having at least one short allele of the serotonin transporter 5-HTTLPR polymorphism had both microstructural white matter abnormalities in frontolimbic networks and a low remission rate(65). Similarly, depressed older patients with the BDNF_{val/val} genotype were less likely to achieve remission than BDNF_{val/met} carriers after 12 weeks of treatment with escitalopram 10 mg daily. However, unlike carriers of the short 5-HTTLPR allele of the serotonin transporter, microstructural abnormalities in the corpus callosum, the left superior corona radiata, and the right inferior longitudinal fasciculus were associated with low remission rate independently of the BDNF allele status.

Studies of brain function identified abnormalities in the cognitive control network that may influence response to antidepressants. Diminished activity in the dorsolateral prefrontal cortex and low functional connectivity between the dorsolateral prefrontal cortex and the dorsal anterior cingulate has been documented in depressed older adults prior to treatment (28). We observed that low resting functional connectivity within a cognitive control network and high functional connectivity within the “default mode” network characterize late-life major depression(66). Beyond this “double dissociation” distinguishing depressed from normal older adults, resting functional connectivity at the cognitive control network,

but not connectivity within the “default mode” network predicted poor remission rate after treatment with escitalopram and persistence of depression, apathy and dysexecutive behavior at the end of treatment. In another study, we showed that large error negative wave (ERN) and a shallow error positive wave (Pe) following the incongruent conditions of an emotional go-nogo task predicted poor response of major late-life depression to escitalopram; the ERN and Pe are thought to reflect different aspects of conflict processing by the anterior cingulate (66).

Improvement of depression is often associated with at least partial normalization of abnormal activation of the anterior cingulate (46, 63, 67–69) and the dorsolateral prefrontal cortex (28). Greater activation of the rostral and dorsal cingulate at baseline predicts better subsequent antidepressant treatment response (70) and that remission of depression is often associated with at least partial normalization of anterior cingulate activation abnormalities (71, 72), and that changes in anterior cingulate function are associated with symptomatic improvement (73).

The prognosis of depression with cognitive impairment

Mild cognitive impairment during episodes of major late-life depression does not progress to dementia in most cases. Instead, it is a stable disturbance that improves only mildly when depressive symptoms are ameliorated (26, 74, 75). However, older patients with major depression and a dementia syndrome that subsides after remission of depression (once termed ‘pseudodementia’) are at high risk for developing irreversible dementia (4, 76–79). Taken together, these studies suggest that between 9–25 per cent of elderly patients with depression and an initially reversible dementia progress into irreversible dementia each year.

Cognitive dysfunction in depressed patients has heterogeneous etiologies and outcomes (59). Some patients presenting with both cognitive dysfunction and late-onset depression, may already have an early stage dementia. This view is supported by findings suggesting that depression is often a prodrome of dementing disorders (4). As discussed above, patients with depression and executive dysfunction, have poor and unstable response to antidepressant treatment (12, 16, 18, 19, 54–56, 80), higher risk of relapse, as well as poorer social and occupational functioning at follow up.

Depression as a risk factor and/or prodrome of dementing disorders

An authoritative meta-analysis of a total sample of more than 100,000 subjects concluded that history of depression doubles the risk for developing dementia in late life (81). Although the effect sizes of individual studies varied, 19 of the 20 studies used in this meta-analysis yielded a positive relationship between history of depression and risk for developing Alzheimer’s disease. Examination of the interval between the occurrence of depression and development of dementia suggested that depression is a risk factor for Alzheimer’s disease rather than a prodrome. This conclusion was consistent with the results of a large study that specifically examined the issue (82). An earlier study (83) focused on studies that included information on family history of dementia and concluded that a lifetime history of depression increased the risk of Alzheimer’s disease, regardless of presence or absence of family history of dementing disorders. Severe depression may confer the highest risk for later development of dementia(84).

In addition to being a risk factor, depressive symptoms are often a prodrome of dementing disorders. In community residing women, depressive symptoms were associated with poorer cognitive function (MMSE, Trails B, Digit Symbol) at baseline and with cognitive decline during a 4 year follow-up (1). Depressed mood at baseline was associated with an increased by three fold risk of incident dementia during a 5 year follow-up elderly community

residents (85). A high prevalence of depressive symptoms and syndromes was observed in individuals with Mild Cognitive Impairment (MCI) both hospital-based studies (median: 44.3%) and in population-based studies (median: 15.7%). The incidence of depressive symptoms varied from 11.7 to 26.6/100 person-years in hospital-based and population-based studies (86). There is evidence that MCI patients with behavioral features are more prone to develop Alzheimer's disease (AD) than patients without these features (87). Taken together the above findings suggest that depression is both a remote risk factor for dementing disorders and a proximal prodromal feature (88).

Several pathogenetic mechanisms have been proposed to account for the relationship between depression and risk for dementing disorders. Vascular disease may play a role in the expression of the clinical symptoms of Alzheimer's disease including depressive symptoms. Vascular disease, Alzheimer's disease and depression have common risk factors (89–91). In addition, inflammatory processes may promote both depression and Alzheimer's disease. Some pro-inflammatory cytokines have been linked to depression, vascular disease, and cognitive compromise (92, 93) and the same cytokines may have direct effects on cognitive status particularly in verbal encoding and memory functions (94). Antidepressants may modify the levels of inflammatory cytokines (95), but it remains unclear whether antidepressants reduce the risk of Alzheimer's disease.

Hypercortisolemia occurring during depressive episodes has been proposed as a factor that may reduce cognitive reserve and promote the expression of cognitive symptoms in patients with dementing disorders. Volumetric studies have found reductions in hippocampal volumes in patients with recurrent major depression (35, 96). Lifetime duration of depression was correlated with hippocampal volume reduction and with behavioral measures of hippocampal function, such as verbal memory (97). The precise relationship between hypercortisolemia, hippocampal volume loss and hippocampal inhibitory control is unknown, although animal studies show that neurotoxic tissue damage may be one possible mechanism.

Another possibility may be that excess and chronic secretion of glucocorticoid hormones can reduce neurotrophic factors, inhibit neurogenesis and render neurons vulnerable to the toxic effect of amyloid. These changes may then compound the neuropathological changes of Alzheimer's disease and accelerate the clinical expression of dementia. The brain-derived neurotrophic factor (BDNF) has been implicated in structural abnormalities of the human hippocampus (98, 99). Several antidepressants elevate BDNF in the rat hippocampus. Recent research suggests that BDNF is rapidly elevated by antidepressant treatments through post-transcriptional mechanisms (100). Through this action, antidepressants may prevent stress-induced inhibition of neurogenesis and increase dendritic branching (101). Whether this action delays the onset, or inhibits the progression of AD is unclear; systematic studies have not yet explored this question.

Can the cognitive deficits of late life depression be mitigated with drug treatment?

Tricyclic antidepressants have not been found to improve cognitive function in depressed older adults. In fact, there is some data to suggest they may worsen cognitive functions. Nortriptyline was shown to compromise verbal learning performance of depressed older adults more than placebo (102). Conversely, some SSRIs may improve cognitive function mainly in patients whose depressive symptoms subside after treatment. Specifically, sertraline has been shown to improve performance on tests of attention, episodic memory, and executive function (103), but only in treatment responders (104). Similarly, depressed older patients with an antidepressant response to citalopram showed improvement in

psychomotor speed, and visuospatial functioning. Conversely, citalopram treatment appeared to have a deleterious effect on neurocognitive functioning in areas of verbal learning and processing speed in patients who remained depressed despite treatment (105).

A substantial number of depressed older patients continue to experience residual depressive symptoms and neuropsychological deficits after antidepressant treatment. Abnormal executive functions, processing speed and working memory persist after remission of mood symptoms in many patients with geriatric depression (106–108). In addition, some demographic variables may leave patients more vulnerable to persistent cognitive dysfunction despite treatment: Old age, high vascular risk score, and low baseline Mini Mental State Examination scores all predicted less cognitive improvement in depressed older adults treated with citalopram (104).

Can cognitive deficits in late life depression be mitigated with cognitive remediation?

The term “cognitive remediation” encompasses a wide variety of interventions. One type of cognitive remediation that we believe has potential to make clinically relevant change relies on the induction of neuroplasticity (N-CCR) and targets brain networks implicated in late life depression. Specifically, symptoms and signs of geriatric depression are thought to be mediated by hypometabolism in dorsal neocortical structures including the DLPFC and dACC, and hypermetabolism of some limbic structures. In this model, abnormalities underlying executive dysfunction may lead to depression directly by promoting the metabolic changes mediating the depressive syndrome or by serving as conditions predisposing to these metabolic changes (109). Therefore, in N-CCR interventions designed to treat geriatric depression, the tasks (games) target and activate dorsal neocortical structures in an attempt to enhance their functioning, and, therefore, improve signs and symptoms of the depression. Although not all CCR tasks induce neuroplasticity in the aging brain, N-CCR tasks (games) are based on activities that have been shown to activate regions of interest, and induce change in the aging brain. To accomplish this goal, N-CCR relies on previous research in induction of neuroplasticity in aging animals to develop principles likely to produce desirable neuroplastic change. N-CCR based on these principles has been applied in treatment trials of aging humans, and has demonstrated that structural and functional change is possible given the right training parameters (50, 110, 111). Recently, we proposed a novel treatment model intended to target and change the functioning of the cerebral networks discussed above through N-CCR (112).

Pathophysiological changes leading to executive dysfunction in geriatric depression may be an appropriate target for N-CCR for geriatric depression for at least three reasons:

First, the targeted executive deficits appear to rely on related cerebral networks, indicating a possible target for intervention.

Second, the selected executive deficits have a relationship to clinical outcomes.

Third, recent research suggests that CCR based on the principles of neuroplastic reorganization can induce neuroplasticity in the aging brain (50, 113).

Older adults show a training-dependent reduction in diffuse brain activation and increases in specific prefrontal areas, which are correlated with improved performance (114), perhaps a result of a change in strategic processing. N-CCR targeting executive functions in older adults has been associated with increased resting cerebral blood flow in the prefrontal cortex (110). Finally, increases in white matter indices (fractional anisotropy and mean diffusivity) in the ACC and the corpus callosum were observed in DTI studies of older adults who underwent N-CCR training, which correlated with improvements in cognitive

performance(111, 115). We suggest that directly targeting and changing the function of cerebral network abnormalities that predispose to poor treatment outcomes is a promising strategy likely to produce neurobiological changes leading to a clinically meaningful improvement of depressive symptoms and cognitive outcomes.

Few recent studies have examined whether CCR can improve cognitive deficits in geriatric depression. Based on the observation that patients with geriatric depression exhibit episodic memory impairment, a few studies have been undertaken training memory function in depressed older adults. In these studies CCR led to improvements in the targeted function (i.e. memory), but no effect on depression, or other clinical symptoms (116).

As we have proposed, CCR targeted to clinically relevant cerebral networks may have implications for treating both cognitive and affective symptoms. To our knowledge, there have been no studies implicating memory impairment in the relationship to remission of symptoms. Further, we have demonstrated previously, that episodic memory impairment in geriatric depression may be at least partially explained by executive dysfunction, specifically the deficient use of verbal strategies (80). Therefore, the study above would be unlikely to address both symptom clusters in geriatric depression. More studies of this nature are needed to help demonstrate whether CCR targeted to clinically relevant neural circuitry is necessary to change both cognitive and affective functioning, or whether more broad training is sufficient.

Conclusion

Major depression in the elderly is often accompanied by cognitive impairment (1) and these cognitive deficits span across multiple cognitive domains(5). Certain cognitive deficits have substantial clinical implications, particularly executive dysfunction (i.e. susceptibility to interference, and semantic strategy). Patients with these deficits are at risk for poor, slow and unstable antidepressant treatment response, relapse, increased risk of suicidality, and current and future disability. Therefore it is important that patients exhibiting deficits in executive functions be identified early in treatment so that appropriate treatment planning can be made.

Mild cognitive impairment emerging during episodes of major late-life depression does not appear to progress to dementia in most cases. Instead, it is a stable disturbance that improves only mildly when depressive symptoms are ameliorated (26, 74, 75). However, history of depression is a risk factor that doubles the likelihood of developing dementia in late life. In addition, depressive symptoms are often a prodrome of dementing disorders. In theory, depression may be viewed as a modifiable risk factor for AD. This view is intriguing, particularly in light of evidence that antidepressants can reduce the levels of inflammatory cytokines (95). However, the possibility that treatment with antidepressants might reduce the risk for AD remains speculative due to the lack of direct studies.

In the majority of patients, pharmacological treatment does not lead to major improvement in cognition. Though there are a few exceptions. There have been reports that tricyclics such as nortryptiline may worsen verbal memory more than placebo placebo(102). Conversely, sertraline and citalopram may improve some cognitive functions, but only in those who respond to treatment(105). In those who do not respond, one study found that citalopram had a deleterious effect on cognition (117).

Last, novel treatment modalities such as neuroplasticity based computerized cognitive remediation seem to show theoretical promise to produce neurobiological changes and ameliorate affective and cognitive symptoms. More studies are needed in this emerging area.

Abbreviations: Cognitive Deficits in Geriatric Depression

DED	depression-executive dysfunction syndrome
I/P	Initiation/Perseveration
DRS	Dementia Rating Scale
CV/IP	Complex Verbal portion of Initiation Preservation
DTI	diffusion tensor imaging
ERN	Large error negative wave
Pe	Shallow error positive wave
MCI	Mild Cognitive Impairment
AD	Alzheimer's disease
BDNF	brain-derived neurotrophic factor

Literature Cited

1. Yaffe K, Blackwell T, Gore R, Sands L, Reus V, Browner WS. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. *Arch Gen Psychiatry*. 1999; 56:425–430. [PubMed: 10232297]
2. Arve S, Tilvis RS, Lehtonen A, Valvanne J, Sairanen S. Coexistence of lowered mood and cognitive impairment of elderly people in five birth cohorts. *Aging (Milano)*. 1999; 11:90–95. [PubMed: 10386168]
3. Bayles, KA.; Kazniak, AW., et al. *Communication and Cognition in Normal Aging and Dementia*. College-Hill Press; San Diego: 1987.
4. Butters MA, Young JB, Lopez O, Aizenstein HJ, Mulsant BH, Reynolds CF 3rd, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci*. 2008; 10:345–357. [PubMed: 18979948]
5. Lockwood KA, Alexopoulos GS, van Gorp WG. Executive dysfunction in geriatric depression. *Am J Psychiatry*. 2002; 159:1119–1126. [PubMed: 12091189]
6. Beats BC, Sahakian BJ, Levy R. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. *Psychol Med*. 1996; 26:591–603. [PubMed: 8733217]
7. Kramer-Ginsberg E, Greenwald BS, Krishnan KR, Christiansen B, Hu J, Ashtari M, et al. Neuropsychological functioning and MRI signal hyperintensities in geriatric depression. *Am J Psychiatry*. 1999; 156:438–444. [PubMed: 10080561]
8. Story TJ, Potter GG, Attix DK, Welsh-Bohmer KA, Steffens DC. Neurocognitive correlates of response to treatment in late-life depression. *Am J Geriatr Psychiatry*. 2008; 16:752–759. [PubMed: 18697883]
9. Boone KB, Lesser I, Miller B, Wohl M, Berman N, Lee A, et al. Cognitive functioning in a mildly to moderately depressed geriatric sample: relationship to chronological age. *J Neuropsychiatry Clin Neurosci*. 1994; 6:267–272. [PubMed: 7950350]
10. Lesser IM, Boone KB, Mehringer CM, Wohl MA, Miller BL, Berman NG. Cognition and white matter hyperintensities in older depressed patients. *Am J Psychiatry*. 1996; 153:1280–1287. [PubMed: 8831435]
11. Elderkin-Thompson V, Kumar A, Mintz J, Boone K, Bahng E, Lavretsky H. Executive dysfunction and visuospatial ability among depressed elders in a community setting. *Arch Clin Neuropsychol*. 2004; 19:597–611. [PubMed: 15271406]
12. Morimoto SS, Gunning FM, Murphy CF, Kanellopoulos D, Kelly RE, Alexopoulos GS. Executive function and short-term remission of geriatric depression: the role of semantic strategy. *Am J Geriatr Psychiatry*. 2011; 19:115–122. [PubMed: 20808124]

13. Butters MA, Whyte EM, Nebes RD, Begley AE, Dew MA, Mulsant BH, et al. The nature and determinants of neuropsychological functioning in late-life depression. *Arch Gen Psychiatry*. 2004; 61:587–595. [PubMed: 15184238]
14. Hart RP, Kwentus JA, Taylor JR, Harkins SW. Rate of forgetting in dementia and depression. *J Consult Clin Psychol*. 1987; 55:101–105. [PubMed: 3571646]
15. Hickie I, Naismith S, Ward PB, Turner K, Scott E, Mitchell P, et al. Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br J Psychiatry*. 2005; 186:197–202. [PubMed: 15738499]
16. Alexopoulos GS, Meyers BS, Young RC, Kalayam B, Kakuma T, Gabrielle M, et al. Executive dysfunction and long-term outcomes of geriatric depression. *Arch Gen Psychiatry*. 2000; 57:285–290. [PubMed: 10711915]
17. Murphy CF, Alexopoulos GS. Longitudinal association of initiation/perseveration and severity of geriatric depression. *Am J Geriatr Psychiatry*. 2004; 12:50–56. [PubMed: 14729559]
18. Potter GG, Kittinger JD, Wagner HR, Steffens DC, Krishnan KR. Prefrontal neuropsychological predictors of treatment remission in late-life depression. *Neuropsychopharmacology*. 2004; 29:2266–2271. [PubMed: 15340392]
19. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry*. 1999; 56:713–718. [PubMed: 10435605]
20. Morimoto SS, Gunning FM, Kanellopoulos D, Murphy CF, Klimstra SA, Kelly RE, et al. Semantic organizational strategy predicts verbal memory and remission rate of geriatric depression. *Int J Geriatr Psychiatry*. 2012; 27:506–512. [PubMed: 21618287]
21. Kiosses DN, Klimstra S, Murphy C, Alexopoulos GS. Executive dysfunction and disability in elderly patients with major depression. *Am J Geriatr Psychiatry*. 2001; 9:269–274. [PubMed: 11481135]
22. Alexopoulos GS, Kiosses DN, Heo M, Murphy CF, Shanmugham B, Gunning-Dixon F. Executive dysfunction and the course of geriatric depression. *Biol Psychiatry*. 2005; 58:204–210. [PubMed: 16018984]
23. Butters MA, Bhalla RK, Mulsant BH, Mazumdar S, Houck PR, Begley AE, et al. Executive functioning, illness course, and relapse/recurrence in continuation and maintenance treatment of late-life depression: is there a relationship? *Am J Geriatr Psychiatry*. 2004; 12:387–394. [PubMed: 15249276]
24. Dombrovski AY, Butters MA, Reynolds CF, Houck PR, Clark L, Mazumdar S, et al. Cognitive performance in suicidal depressed elderly: preliminary report. *Am J Geriatr Psychiatry*. 2008; 16:109–115. [PubMed: 18239196]
25. Dombrovski AY, Clark L, Siegle GJ, Butters MA, Ichikawa N, Sahakian BJ, et al. Reward/Punishment reversal learning in older suicide attempters. *Am J Psychiatry*. 2010; 167:699–707. [PubMed: 20231320]
26. Alexopoulos GS, Kiosses DN, Murphy C, Heo M. Executive dysfunction, heart disease burden, and remission of geriatric depression. *Neuropsychopharmacology*. 2004; 29:2278–2284. [PubMed: 15340393]
27. Murphy CF, Gunning-Dixon FM, Hoptman MJ, Lim KO, Ardekani B, Shields JK, et al. White-matter integrity predicts stroop performance in patients with geriatric depression. *Biol Psychiatry*. 2007; 61:1007–1010. [PubMed: 17123478]
28. Aizenstein HJ, Butters MA, Wu M, Mazurkewicz LM, Stenger VA, Gianaros PJ, et al. Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. *Am J Geriatr Psychiatry*. 2009; 17:30–42. [PubMed: 19001356]
29. Van Otterloo E, O'Dwyer G, Stockmeier CA, Steffens DC, Krishnan RR, Rajkowska G. Reductions in neuronal density in elderly depressed are region specific. *Int J Geriatr Psychiatry*. 2009; 24:856–864. [PubMed: 19405038]
30. Ballmaier M, Toga AW, Blanton RE, Sowell ER, Lavretsky H, Peterson J, et al. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. *Am J Psychiatry*. 2004; 161:99–108. [PubMed: 14702257]

31. Yuan Y, Zhu W, Zhang Z, Bai F, Yu H, Shi Y, et al. Regional gray matter changes are associated with cognitive deficits in remitted geriatric depression: an optimized voxel-based morphometry study. *Biol Psychiatry*. 2008; 64:541–544. [PubMed: 18550031]
32. Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–827. [PubMed: 9126739]
33. Krishnan KR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, et al. Magnetic resonance imaging of the caudate nuclei in depression. Preliminary observations. *Arch Gen Psychiatry*. 1992; 49:553–557. [PubMed: 1627046]
34. Husain MM, McDonald WM, Doraiswamy PM, Figiel GS, Na C, Escalona PR, et al. A magnetic resonance imaging study of putamen nuclei in major depression. *Psychiatry Res*. 1991; 40:95–99. [PubMed: 1763144]
35. Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci U S A*. 1996; 93:3908–3913. [PubMed: 8632988]
36. Lai T, Payne ME, Byrum CE, Steffens DC, Krishnan KR. Reduction of orbital frontal cortex volume in geriatric depression. *Biol Psychiatry*. 2000; 48:971–975. [PubMed: 11082470]
37. Sheline YI, Gado MH, Price JL. Amygdala core nuclei volumes are decreased in recurrent major depression. *Neuroreport*. 1998; 9:2023–2028. [PubMed: 9674587]
38. Boone KB, Miller BL, Lesser IM, Mehringer CM, Hill-Gutierrez E, Goldberg MA, et al. Neuropsychological correlates of white-matter lesions in healthy elderly subjects. A threshold effect. *Arch Neurol*. 1992; 49:549–554. [PubMed: 1580819]
39. Kumar A, Bilker W, Jin Z, Udupa J. Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. *Neuropsychopharmacology*. 2000; 22:264–274. [PubMed: 10693154]
40. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, et al. Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry*. 2008; 165:238–244. [PubMed: 18172016]
41. Gunning-Dixon FM, Hoptman MJ, Lim KO, Murphy CF, Klimstra S, Latoussakis V, et al. Macromolecular white matter abnormalities in geriatric depression: a magnetization transfer imaging study. *Am J Geriatr Psychiatry*. 2008; 16:255–262. [PubMed: 18378551]
42. MacFall JR, Payne ME, Provenzale JE, Krishnan KR. Medial orbital frontal lesions in late-onset depression. *Biol Psychiatry*. 2001; 49:803–806. [PubMed: 11331089]
43. Hannestad J, Taylor WD, McQuoid DR, Payne ME, Krishnan KR, Steffens DC, et al. White matter lesion volumes and caudate volumes in late-life depression. *Int J Geriatr Psychiatry*. 2006; 21:1193–1198. [PubMed: 16955447]
44. Wu JC, Gillin JC, Buchsbaum MS, Hershey T, Johnson JC, Bunney WE Jr. Effect of sleep deprivation on brain metabolism of depressed patients. *Am J Psychiatry*. 1992; 149:538–543. [PubMed: 1554042]
45. Drevets WC. Prefrontal cortical-amygdalar metabolism in major depression. *Ann N Y Acad Sci*. 1999; 877:614–637. [PubMed: 10415674]
46. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol*. 2002; 12:527–544. [PubMed: 12468016]
47. Drevets WC. Functional neuroimaging studies of depression: the anatomy of melancholia. *Annu Rev Med*. 1998; 49:341–361. [PubMed: 9509268]
48. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. *J Neurosci*. 1992; 12:3628–3641. [PubMed: 1527602]
49. Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ. The anatomy of melancholia--focal abnormalities of cerebral blood flow in major depression. *Psychol Med*. 1992; 22:607–615. [PubMed: 1410086]
50. Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, et al. A cognitive training program based on principles of brain plasticity: results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) study. *J Am Geriatr Soc*. 2009; 57:594–603. [PubMed: 19220558]

51. Alexopoulos GS, Katz IR, Reynolds CF, Ross RW. Depression in older adults. *J Psychiatr Pract*. 2001; 7:441–446. [PubMed: 15990559]
52. Alexopoulos GS, Vrontou C, Kakuma T, Meyers BS, Young RC, Klausner E, et al. Disability in geriatric depression. *Am J Psychiatry*. 1996; 153:877–885. [PubMed: 8659609]
53. Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO. Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry*. 2002; 159:1929–1932. [PubMed: 12411231]
54. Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry*. 2007; 15:553–563. [PubMed: 17586780]
55. Sneed JR, Keilp JG, Brickman AM, Roose SP. The specificity of neuropsychological impairment in predicting antidepressant non-response in the very old depressed. *Int J Geriatr Psychiatry*. 2008; 23:319–323. [PubMed: 17726720]
56. Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychol Med*. 1998; 28:1015–1026. [PubMed: 9794009]
57. Alexopoulos GS. Role of executive function in late-life depression. *J Clin Psychiatry*. 2003; 64(Suppl 14):18–23. [PubMed: 14658931]
58. McLennan SN, Mathias JL. The depression-executive dysfunction (DED) syndrome and response to antidepressants: a meta-analytic review. *Int J Geriatr Psychiatry*. 2010; 25:933–944. [PubMed: 20872927]
59. Alexopoulos GS, Kiosses DN, Klimstra S, Kalayam B, Bruce ML. Clinical presentation of the “depression-executive dysfunction syndrome” of late life. *Am J Geriatr Psychiatry*. 2002; 10:98–106. [PubMed: 11790640]
60. Lezak, MD. *Neuropsychological assessment*. New York: Oxford University Press; 1976.
61. Benton, AL. *Contributions to neuropsychological assessment: a clinical manual*. 2. New York: Oxford University Press; 1994.
62. Elderkin-Thompson V, Hellemann G, Pham D, Kumar A. Prefrontal brain morphology and executive function in healthy and depressed elderly. *Int J Geriatr Psychiatry*. 2008
63. Kennedy SH, Evans KR, Krüger S, Mayberg HS, Meyer JH, McCann S, et al. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am J Psychiatry*. 2001; 158:899–905. [PubMed: 11384897]
64. Alexopoulos GS, Glatt CE, Hoptman MJ, Kanellopoulos D, Murphy CF, Kelly RE, et al. BDNF val66met polymorphism, white matter abnormalities and remission of geriatric depression. *J Affect Disord*. 2010; 125:262–268. [PubMed: 20346518]
65. Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Glatt CE, Latoussakis V, Kelly RE, et al. Serotonin transporter polymorphisms, microstructural white matter abnormalities and remission of geriatric depression. *J Affect Disord*. 2009; 119:132–141. [PubMed: 19375170]
66. Alexopoulos GS, Hoptman MJ, Kanellopoulos D, Murphy CF, Lim KO, Gunning FM. Functional connectivity in the cognitive control network and the default mode network in late-life depression. *J Affect Disord*. 2012; 139:56–65. [PubMed: 22425432]
67. Buchsbaum MS, Wu J, Siegel BV, Hackett E, Trenary M, Abel L, et al. Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry*. 1997; 41:15–22. [PubMed: 8988791]
68. Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, et al. Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. *Arch Gen Psychiatry*. 2002; 59:250–261. [PubMed: 11879163]
69. Gildengers AG, Houck PR, Mulsant BH, Dew MA, Aizenstein HJ, Jones BL, et al. Trajectories of treatment response in late-life depression: psychosocial and clinical correlates. *J Clin Psychopharmacol*. 2005; 25:S8–13. [PubMed: 16027561]
70. Langenecker SA, Kennedy SE, Guidotti LM, Briceno EM, Own LS, Hooven T, et al. Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry*. 2007; 62:1272–1280. [PubMed: 17585888]

71. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry*. 1999; 156:675–682. [PubMed: 10327898]
72. Wu J, Buchsbaum MS, Gillin JC, Tang C, Cadwell S, Wiegand M, et al. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. *Am J Psychiatry*. 1999; 156:1149–1158. [PubMed: 10450253]
73. Fu CH, Williams SC, Cleare AJ, Brammer MJ, Walsh ND, Kim J, et al. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Arch Gen Psychiatry*. 2004; 61:877–889. [PubMed: 15351766]
74. Murphy CF, Alexopoulos GS. Attention network dysfunction and treatment response of geriatric depression. *J Clin Exp Neuropsychol*. 2006; 28:96–100. [PubMed: 16448978]
75. Nakano Y, Baba H, Maeshima H, Kitajima A, Sakai Y, Baba K, et al. Executive dysfunction in medicated, remitted state of major depression. *J Affect Disord*. 2008; 111:46–51. [PubMed: 18304646]
76. Reynolds CF, Kupfer DJ, Hoch CC, Stack JA, Houck PR, Sewitch DE. Two-year follow-up of elderly patients with mixed depression and dementia. Clinical and electroencephalographic sleep findings. *J Am Geriatr Soc*. 1986; 34:793–799. [PubMed: 3771979]
77. Kral VA, Emery OB. Long-term follow-up of depressive pseudodementia of the aged. *Can J Psychiatry*. 1989; 34:445–446. [PubMed: 2766198]
78. Copeland JR, Davidson IA, Dewey ME, Gilmore C, Larkin BA, McWilliam C, et al. Alzheimer's disease, other dementias, depression and pseudodementia: prevalence, incidence and three-year outcome in Liverpool. *Br J Psychiatry*. 1992; 161:230–239. [PubMed: 1521106]
79. Alexopoulos GS, Meyers BS, Young RC, Mattis S, Kakuma T. The course of geriatric depression with "reversible dementia": a controlled study. *Am J Psychiatry*. 1993; 150:1693–1699. [PubMed: 8105707]
80. Morimoto SS, Gunning FM, Kanellopoulos D, Murphy CF, Klimstra SA, Kelly RE Jr, et al. Semantic organizational strategy predicts verbal memory and remission rate of geriatric depression. *International journal of geriatric psychiatry*. 2011
81. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Arch Gen Psychiatry*. 2006; 63:530–538. [PubMed: 16651510]
82. Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. *Arch Neurol*. 2003; 60:753–759. [PubMed: 12756140]
83. van Duijn CM, Hendriks L, Farrer LA, Backhovens H, Cruts M, Wehnert A, et al. A population-based study of familial Alzheimer disease: linkage to chromosomes 14, 19, and 21. *Am J Hum Genet*. 1994; 55:714–727. [PubMed: 7942850]
84. Chen R, Hu Z, Wei L, Qin X, McCracken C, Copeland JR. Severity of depression and risk for subsequent dementia: cohort studies in China and the UK. *Br J Psychiatry*. 2008; 193:373–377. [PubMed: 18978315]
85. Devanand DP, Sano M, Tang MX, Taylor S, Gurland BJ, Wilder D, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. *Arch Gen Psychiatry*. 1996; 53:175–182. [PubMed: 8629893]
86. Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, et al. Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am J Geriatr Psychiatry*. 2010; 18:98–116. [PubMed: 20104067]
87. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dement Geriatr Cogn Disord*. 2008; 25:115–126. [PubMed: 18087152]
88. Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. *Biol Psychiatry*. 2002; 52:543–558. [PubMed: 12361668]

89. Alexopoulos GS. The vascular depression hypothesis: 10 years later. *Biol Psychiatry*. 2006; 60:1304–1305. [PubMed: 17157096]
90. Iadecola C, Gorelick PB. Converging pathogenic mechanisms in vascular and neurodegenerative dementia. *Stroke*. 2003; 34:335–337. [PubMed: 12574528]
91. Rasgon N, Jarvik L. Insulin resistance, affective disorders, and Alzheimer's disease: review and hypothesis. *J Gerontol A Biol Sci Med Sci*. 2004; 59:178–183. discussion 184–192. [PubMed: 14999034]
92. Alexopoulos GS, Morimoto SS. The inflammation hypothesis in geriatric depression. *Int J Geriatr Psychiatry*. 2011
93. Morimoto SS, Alexopoulos GS. Immunity, aging, and geriatric depression. *Psychiatr Clin North Am*. 2011; 34:437–449. ix. [PubMed: 21536167]
94. Elderkin-Thompson V, Irwin MR, Hellemann G, Kumar A. Interleukin-6 and memory functions of encoding and recall in healthy and depressed elderly adults. *Am J Geriatr Psychiatry*. 2012; 20:753–763. [PubMed: 22892560]
95. Castanon N, Leonard BE, Neveu PJ, Yirmiya R. Effects of antidepressants on cytokine production and actions. *Brain Behav Immun*. 2002; 16:569–574. [PubMed: 12401470]
96. Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. *Am J Psychiatry*. 2003; 160:1516–1518. [PubMed: 12900317]
97. Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999; 19:5034–5043. [PubMed: 10366636]
98. Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. *J Neurosci*. 2004; 24:10099–10102. [PubMed: 15537879]
99. Bueller JA, Aftab M, Sen S, Gomez-Hassan D, Burmeister M, Zubietta JK. BDNF Val66Met allele is associated with reduced hippocampal volume in healthy subjects. *Biol Psychiatry*. 2006; 59:812–815. [PubMed: 16442082]
100. Musazzi L, Cattaneo A, Tardito D, Barbon A, Gennarelli M, Barlati S, et al. Early raise of BDNF in hippocampus suggests induction of posttranscriptional mechanisms by antidepressants. *BMC Neurosci*. 2009; 10:48. [PubMed: 19439074]
101. Duman RS, Heninger GR, Nestler EJ. A molecular and cellular theory of depression. *Arch Gen Psychiatry*. 1997; 54:597–606. [PubMed: 9236543]
102. Meyers BS, Mattis S, Gabriele M, Kakuma T. Effects of nortriptyline on memory selfassessment and performance in recovered elderly depressives. *Psychopharmacol Bull*. 1991; 27:295–299. [PubMed: 1775602]
103. Barch DM, D'Angelo G, Pieper C, Wilkins CH, Welsh-Bohmer K, Taylor W, et al. Cognitive improvement following treatment in late-life depression: relationship to vascular risk and age of onset. *Am J Geriatr Psychiatry*. 2012; 20:682–690. [PubMed: 22430020]
104. Devanand DP, Pelton GH, Marston K, Camacho Y, Roose SP, Stern Y, et al. Sertraline treatment of elderly patients with depression and cognitive impairment. *Int J Geriatr Psychiatry*. 2003; 18:123–130. [PubMed: 12571820]
105. Culang ME, Sneed JR, Keilp JG, Rutherford BR, Pelton GH, Devanand DP, et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. *Am J Geriatr Psychiatry*. 2009; 17:881–888. [PubMed: 19916207]
106. Nebes RD, Pollock BG, Houck PR, Butters MA, Mulsant BH, Zmuda MD, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, doubleblind clinical trial with nortriptyline and paroxetine. *Journal of psychiatric research*. 2003; 37:99–108. [PubMed: 12842163]
107. Butters MA, Becker JT, Nebes RD, Zmuda MD, Mulsant BH, Pollock BG, et al. Changes in cognitive functioning following treatment of late-life depression. *Am J Psychiatry*. 2000; 157:1949–1954. [PubMed: 11097959]
108. Aizenstein HJ, Butters MA, Wu M, Mazurkewicz LM, Stenger VA, Gianaros PJ, et al. Altered Functioning of the Executive Control Circuit in Late-Life Depression: Episodic and Persistent Phenomena. *Am J Geriatr Psychiatry*. 2008

109. Alexopoulos GS. Depression in the elderly. *Lancet*. 2005; 365:1961–1970. [PubMed: 15936426]
110. Mozolic JL, Hayasaka S, Laurienti PJ. A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Front Hum Neurosci*. 2010; 4:16. [PubMed: 20300200]
111. Lovden M, Bodammer NC, Kuhn S, Kaufmann J, Schutze H, Tempelmann C, et al. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*. 2010; 48:3878–3883. [PubMed: 20816877]
112. Morimoto SS, Wexler BE, Alexopoulos GS. Neuroplasticity-based computerized cognitive remediation for geriatric depression. *Int J Geriatr Psychiatry*. 2012; 27:1239–1247. [PubMed: 22451346]
113. Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci U S A*. 2006; 103:12523–12528. [PubMed: 16888038]
114. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging*. 2007; 28:272–283. [PubMed: 16480789]
115. Takeuchi H, Sekiguchi A, Taki Y, Yokoyama S, Yomogida Y, Komuro N, et al. Training of working memory impacts structural connectivity. *J Neurosci*. 2010; 30:3297–3303. [PubMed: 20203189]
116. Naismith SL, Redoblado-Hodge MA, Lewis SJ, Scott EM, Hickie IB. Cognitive training in affective disorders improves memory: a preliminary study using the NEAR approach. *Journal of affective disorders*. 2010; 121:258–262. [PubMed: 19616856]
117. Sneed JR, Culang ME, Keilp JG, Rutherford BR, Devanand DP, Roose SP. Antidepressant medication and executive dysfunction: a deleterious interaction in late-life depression. *Am J Geriatr Psychiatry*. 2010; 18:128–135. [PubMed: 20104069]

Key Points

- Major depression in the elderly is often accompanied by cognitive impairment that span multiple cognitive domains.
- Patients with executive dysfunction are at risk for poor, slow and unstable antidepressant treatment response, relapse, increased risk of suicidality, and current and future disability.
- Mild cognitive impairment emerging during episodes of major late-life depression does not appear to progress to dementia in most cases.
- History of depression is a risk factor that doubles the likelihood of developing dementia in late life.
- In the majority of patients, pharmacological treatment does not lead to major improvement in cognition, though there are reports that indicate beneficial or deleterious effect on cognition from tricyclics, sertraline, and citalopram.