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Diagnosis and Treatment of Depression and Cognitive Impairment in Late-Life

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Abstract

Cognitive impairment in late life depression is prevalent, disabling, and heterogeneous. Although mild cognitive impairment in depression does not usually progress to dementia, accurate assessment of cognition is vital to prognosis and treatment planning. For example, executive dysfunction often accompanies late-life depression, influences performance across cognitive domains, and is associated with poor antidepressant treatment outcomes. Here, we review how assessment can capture dysfunction across cognitive domains, and discuss cognitive trajectories frequently observed in late-life depression in the context of the neurobiology of this disorder. Furthermore we review the efficacy of a sample of interventions tailored to specific cognitive profiles.

Keywords

Geriatric Depression; Cognitive Impairment; Older Adults; Cognitive Control; Psychotherapy; Antidepressants

Introduction

Major depression in the elderly often presents with cognitive impairment. Mild cognitive deficits in memory, processing speed and executive functioning are particularly common in late-life depression[1, 2]. Executive functions are control mechanisms that modulate aspects of emotion and cognition, and disruption to these processes is associated with poor course of illness and worse clinical outcomes of late-life depression[3–7]. In some cases, depression may present concomitantly with[8], or even precede[9], dementing disorders characterized by diffuse cognitive deficits. The variability in the cognitive profile of geriatric depression suggests this syndrome represents a heterogeneous group of disorders requiring careful treatment planning and close neuropsychiatric follow-up. In this review, we discuss the relevance of cognitive impairment to the care of geriatric depression. We do so by first describing the various cognitive trajectories and associated clinical manifestations of cognitive impairment

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in these disorders. We next discuss current assessment and treatment practices and recommendations for clinicians treating patients with late-life depression.

Cognitive Impairments in Late-Life Depression

Major depressive disorder in the elderly is accompanied by structural and functional abnormalities in the frontal lobes and their connections with limbic and striatal systems (see 10–11 for detailed reviews)[10, 11]. Disruption of the "cognitive control network" is especially prominent; this network encompasses the dorsolateral prefrontal cortex, dorsal and rostral regions of the anterior cingulate, and parietal association regions[12, 13]. Clinically, cognitive control network disruption results in symptoms of executive dysfunction, including a tendency to attend to irrelevant information, impaired concentration, disorganization, difficulty shifting attention, and perseveration, or the inability to disengage from earlier behavioral responses[10]. Roughly 30–40% of non-demented older adults with major depression exhibit signs of executive dysfunction on cognitive examination[10, 14]. Depressed older adults often perform poorly on tests of verbal fluency, the Wisconsin Card Sorting Test (a measure of problem solving and cognitive flexibility), the Tower of London (a test of planning) and the Stroop Color Word Interference Test (a measure of cognitive inhibition)[15]. Other executive functions, including planning and semantic organization, may account for observed deficits in select aspects of episodic memory and visuospatial abilities[16, 17]. For example, geriatric depression patients frequently perform poorly on word-list memory and recall, mediated by executive functioning, while memory on recognition and cued recall conditions and narrative contextual memory, tasks that do not depend on executive functions, are often intact[16,18].

"Depression with Reversible Dementia" Syndrome

Some older adults with late-life depression may develop a dementia syndrome (previously termed "pseudodementia"), i.e. a cognitive impairment reaching the severity of dementia but subsides upon remission of depression. These patients usually present with a severe, late-onset depression and a mild dementia syndrome. When compared with depressed patients with Alzheimer's Disease (AD), patients with depression and "reversible dementia" exhibit more psychic and somatic anxiety, early morning awakening, and loss of libido[19]. Although the dementia syndrome subsides after remission of depression, a large percentage of patients with depression with "reversible dementia" progress into irreversible dementia within 2–3 years[20].

Cognitive Impairment and Clinical Outcomes in Late-Life Depression

Cognitive control dysfunction is associated with poor response of geriatric depression to antidepressants. Poor performance on measures of executive functioning, such as verbal fluency and cognitive inhibition, predict poor and slow antidepressant response, relapse, and greater levels of functional disability[3,721–23]. Poor performance on tests of cognitive control is associated with greater lethality of suicide attempts in older adults[24, 25]. We found that impaired performance in semantic organization during a verbal fluency task from the Dementia Rating Scale, a global screening test of cognitive functioning, predicted poor treatment response in depressed older patients[4]. These findings were statistically

independent of processing speed. We followed up these findings with a second study that demonstrated deficits in that semantic organizational strategy use (clustering "like" words together during recall) on a verbal memory task accounted for both verbal memory performance and treatment response[26]. These studies showed that semantic organization predicts poor response to antidepressant drug treatment regardless of the task by which it is elicited[26].

Failure to achieve remission following treatment with escitalopram in late-life depression is associated with decreased grey matter volume in the dorsal and rostral anterior cingulate[27], and microstructural white matter abnormalities likely contributing to disconnection between these brain regions and to poor treatment response[28]. In late-life depression low functional connectivity between the anterior cingulate cortex and the dorsolateral prefrontal cortex has been found to be associated with poor remission rate during treatment with escitalopram[12].

Prognosis of Cognitive Impairment in Late-Life Depression

Mild cognitive impairment during depressive episodes in late-life does not progress to dementia in most cases. Instead, it is often a stable disturbance that either persists or improves only when depressive symptoms are ameliorated[3, 29–31]. However, severe cognitive symptoms in geriatric depression patients do appear to result in an increased risk for developing dementia[20]. The variability in the cognitive abnormalities seen in geriatric depression suggests that this syndrome represents heterogeneous disorders[29]. Many depressed older adults do not have significant cognitive impairment[2]. In those with depression and cognitive impairment, the two syndromes may have a common cause (e.g., vascular disease[11]) or simply co-exist and have distinct causes (e.g. a recurrence of early-onset depression in an older patient with early stage Alzheimer's disease)[8]. Depressive symptoms may also be a prodrome (early symptom) of a dementing disorder. Finally, depressive disorder with onset in early life can be a risk factor for both Alzheimer's disease and vascular dementia[30–32].

Neuropsychological assessment can aid the differential diagnosis of geriatric patients with depression and cognitive impairment (Table 1). Notably, select cognitive deficits may help differentiate depressed patients who are likely to experience cognitive decline compared to depressed patients who remain cognitively stable. Rushing et al.[9] contrasted baseline performance on multiple cognitive measures and found that only recall of narrative contextual information (i.e., short stories) predicted conversion to dementia in the 15 out of 120 older adults with major depression who developed Alzheimer's disease up to 13 years later. Tests of executive functioning and executive-dependent word-list recall did not add significant value to the dementia prediction model. Thus, impaired memory for verbal contextual information, dependent on intact hippocampal functioning, may predict conversion to Alzheimer's disease in geriatric depression, whereas mild impairment in frontally mediated executive functions may not. This is consistent with evidence from non-depressed older adults, namely that the amnestic subtype of mild cognitive impairment, is associated with a progression to Alzheimer's disease whereas the dysexecutive subtype is associated with vascular disease[33].

Evaluation of Cognitive Impairment in the Elderly

Evaluation of depressive syndromes in cognitively impaired patients is complicated by the symptom overlap with dementia, the instability of depressive symptoms over time, and the poor ability of elderly patients to report their symptoms. If criteria for one of the depressive syndromes are met, an antidepressant treatment trial should be offered[37]. Beyond the benefits of alleviating the suffering and complications of depression, remission of the depressive syndrome can increase the clinician's ability to evaluate the severity of the remaining cognitive impairment and plan for further treatment and follow up. Screening tests and questionnaires can be useful to detect select aspects of cognitive impairment. While the Mini Mental State Examination (MMSE), and Montreal Cognitive Assessment (Table 1) are relatively ubiquitous screening measures for gross cognitive impairment other instruments including the Mattis Dementia Rating scale (DRS-2) (Table 1)[34] and Executive Interview (EXIT)[35] may be more sensitive to generalized cognitive decline[36]. The Cornell Scale for Depression in Dementia may also aid in quantifying depressive symptoms and signs; this scale integrates informant with patient reports[37]. Among patients with suspected executive dysfunction who perform well on traditional measures of executive functioning, the Frontal Systems Behavior Scale (FrSBe)[38] can help characterize behavioral manifestations of executive deficits. For instance, on the FrSBe, patients and informants rate the presence of behavioral syndromes of apathy and disinhibition as well as difficulties in working memory, planning, sequencing, organizing, and abstracting. In addition to characterizing executive dysfunction, preliminary evidence suggests that behavioral abnormalities identified by the FrSBe are associated with slower response of late-life depression to escitalopram[39]. The usefulness of screening measures and questionnaires is limited in situations where the cognitive deficits are subtle, there is concern about a comorbid dementia or the patient and/or family member is not a reliable informant in the case of questionnaires. In such cases, clinicians concerned about cognitive dysfunction should refer for a neurological and/or neuropsychological consultation (see Table 1 for examples of cognitive functions that should be assessed)[40]. Variability in the course of elders with depression and cognitive impairment suggests the need for careful follow up.

Pharmacologic Treatment

The Expert Consensus Guideline recommends antidepressant drug therapy combined with a psychosocial intervention as the treatment of choice for geriatric depression[41]. Tricyclic antidepressants have not been found to improve cognitive function in depressed older adults. In fact, nortriptyline was shown to compromise verbal learning performance of depressed older adults more than placebo[42]. Conversely, some Selective Serotonin Reuptake Inhibitors (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, but only in treatment responders[43]. Similarly, depressed older patients with an antidepressant response to citalopram showed improvement in psychomotor speed and visuospatial functioning. However, citalopram treatment appeared to worsen verbal learning and processing speed in patients who remained depressed despite treatment[44]. In contrast there is mounting preliminary evidence from both animal and human studies[45, 46] showing improvement of

both mood and cognitive functioning with vortioxetene; however, studies in humans are limited, and additional research is needed in humans to substantiate effects on cognition.

Nevertheless, 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[47–49]. 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[43].

Treatment of depression with sertraline[50] or mirtazapine[51] in Alzheimer's disease does not improve depressive symptoms more than placebo. Further, SSRI treatment is also associated with increased adverse events suggesting that their use for first-line treatment for depression should be reconsidered[51].

Psychotherapies for Late-Life Depression with Cognitive

Impairment Non-pharmacological interventions should be considered in conjunction with pharmacotherapy or given alone in depression of mild to moderate severity[52]. Specific psychotherapies have also been developed to remedy the behavioral deficits of depressed older adults with cognitive impairments associated with poor response to antidepressants (see Table 2[53–60]). As an example, problem-solving therapy (PST) was modified to address the behavioral deficits of patients with late-life depression and executive dysfunction[61] and has been efficacious in reducing depression and disability in cognitively unimpaired depressed older adults and in older adults with cognitive impairment[53, 54, 62]. PST is based on the premise that helping patients become better managers of their lives reduces stress and thus ameliorates depression. Patients are instructed to identify problems, brainstorm different ways to solve problems, create action plans, perform a cost-benefit analysis, and evaluate the effectiveness of potential solutions. PST improves skills needed in interpersonal relationships, remedies communication deficits, and increases behavioral activation by enhancing exposure to pleasurable activities. Further, recently therapies have been developed for depressed elderly patients that incorporate the modification of the patient's environment or "ecosystem" which includes the patient, the caregiver, and the patient's home environment (see 'EFT' Table 2) [57]. In addition to utilizing PST as a basic therapeutic framework, Problem Adaptation Therapy or PATH (Table 2) integrates environmental adaptation tools and the primary caregiver to help the patient circumvent their cognitive impairment and engage in problem resolution and adaptive functioning[53].

Computerized Cognitive Remediation

Certain types of computerized cognitive remediation can improve brain functioning by inducing neuroplasticity (nCCR).[63, 64] We have proposed that computerized cognitive remediation that relies on the induction of neuroplasticity and targets brain networks associated with clinical outcomes in late life depression has the potential to improve treatment response. Recently, we developed a novel treatment model using nCCR to

improve the functioning of cerebral networks responsible for executive functioning and associated with poor response to antidepressants[65]. Our nCCR treatment model is based on the assumption that neuroplastic changes that improve the function of cerebral network abnormalities contributing to antidepressant resistance (i.e. dorsal neocortical structures participating in the cognitive control network) would improve symptoms and signs of late-life depression. Preliminary evidence suggests that nCCR treatment induces a clinically meaningful improvement of both cognitive and affective symptoms in depressed elderly patients who failed to remit using conventional antidepressants. In fact 72% of patients reached remission after 4 weeks of treatment with nCCR.[66]

Future Investigations

Classic neuropsychological tests of executive functioning primarily assess the cognitive control network and offer little information on the ventromedial prefrontal regions. Ventromedial prefrontal regions, including the orbitofrontal cortex, ventral-rostral anterior cingulate, and their connections with the amygdala, mediate divergent functions such as processing of emotional information, utilization of cues in the environment to predict rewarding or aversive events, and the regulation of behavioral responses[67]. The ventromedial region also mediates reward-related decision-making, a complex task involving option generation, evaluation of risks and consequences, and choice of a course of action[68]. Ventromedial dysfunction is prominent in major depression[69], yet ventromedial behavioral abnormalities have seldom been investigated in late-life depression. We recently treated an elderly woman with major depression who presented with mood lability, distractibility, poor self-monitoring, and impulsivity, yet demonstrated no impairment on classic tests of executive function[70]. Ventromedial behavioral disturbances, potentially dissociable from cognitive control dysfunction, may characterize a subgroup of late-life depression patients whose neurobiology, treatment response, and course of illness require further investigation.

The need to assess ventromedial functioning led to the development of Stroop-like emotional conflict tasks (e.g., categorizing facial affect while ignoring overlaid affect label words)[71] and decision-making paradigms, such as the Iowa Gambling Task.[72] When performing the Iowa, individuals select cards, one at a time, from one of four decks. Half of the decks are disadvantageous (i.e, higher immediate rewards but long-term negative outcomes) and the other half is advantageous (i.e., lower immediate rewards but long-term positive outcomes). Overall, older adults with major depression do not differ from age-matched controls on the Iowa or other gambling paradigms.[73, 74] However, older adults with major depression and clinical evidence of poor decision-making (as evidenced by a history of attempted suicide) perform worse on a gambling task when compared to older depressed adults with no history of suicide.[73] In contrast, apathetic, depressed elderly patients are not influenced by immediate reinforcers (the high rewards of the disadvantageous decks)and demonstrate an advantageous strategy on the Iowa Gambling Task (selecting cards from the conservative decks) when compared to non-apathetic, depressed older adults.[74] Elucidating the neurocognitive outcome of geriatric depression patients with ventromedial disturbance remains ongoing.

Conclusions

Major depression in the elderly is often accompanied by impairment[75] spanning across multiple cognitive domains[14]. Most depressed older adults do not develop neurodegenerative diseases, yet some cases of late-onset depression represent the first behavioral abnormalities of dementia syndromes. In some cases, depression and cognitive impairment may be related to a single underlying illness, e.g. cerebrovascular disease, in others, neurodevelopmental disease and depression simply coexist. Deficits in executive functions (i.e. susceptibility to interference, and semantic strategy) have important clinical implications such as: Poor, slow and unstable response of depression to antidepressant drugs, early relapse and recurrence, increased risk of suicidality, and disability disproportional to the severity of depression. In the majority of patients, pharmacological treatment does not lead to major improvement in cognition. Though there are a few exceptions. Therefore, it is important to clarify the patients' cognitive status early so that appropriate treatment recommendations can be made.

Psychotherapies have been developed to address the behavioral deficits of depression with executive dysfunction (PST), as well as in patients with depression and dementia (PATH) and patients with post-stroke depression (EFT). These approaches have been found to be effective to improve depression and disability. Neuroplasticity based computerized cognitive remediation targeting brain networks responsible for executive functioning has been developed, and preliminary studies are encouraging. More studies are needed in this emerging area.

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Table 1

Clinical Assessment of Cognitive Function: Sample of Cognitive Domains, Measures, and Associated Cognitive Functions[1]

Cognitive Function	Bedside Examination	Neuropsychological tests	
		Measure:	**Cognitive Function:**
General Cognitive Function	Mini Mental State Examination (MMSE) Montreal Cognitive Assessment (MOCA)	Dementia Rating Scale - 2 (DRS-2) Repeatable Battery for Assessment of Neuropsychological Status (RBANS)	
Attention	Cannot hold a telephone number in mind Easily distracted Tasks take too long Poor concentration	Digit Span (WAIS-IV) Brief Test of Attention (BTA) Digit Symbol & Coding Letter-Number Sequencing (WAIS-IV)	Auditory Attention/Working Memory Auditory Attention Divided Attention/Working Memory Working Memory
Memory	Poor recall of recent events Need of reminders Repeats self	Benton Visuospatial Memory Test-Revised (BVMT-R) California Verbal Learning Test-II (CVLT-II) Hopkin's Verbal Learning Test – Revised (HVLT-R) Logical Memory Subtest (WMS-IV)	Non-Verbal Learning & Memory Verbal List Learning & Memory Verbal List Learning & Memory Verbal Contextual Learning & Memory
Language	Word-finding difficulty Use of vague generic terms Syntactic errors Comprehension difficulty Difficulty keeping up with conversation.	Boston Naming Test -2 (BNT-2) Token Test Boston Diagnostic Aphasia Examination – 3rd Edition (BDAE-3) Animal Naming Test Controlled Oral Word Association Test (COWAT)	Confrontation Naming Comprehension Comprehensive Language Assessment Semantic Fluency Phonemic Fluency
Praxis, Somatosensory & Motor Functions	Difficulty with use of familiar tools (e.g., pen, toothbrush) Difficulty with sequencing of actions (e.g., show me how you would cut your meat?)	Apraxia Exam Right-Left Orientation Finger Localization Finger Tapping Test Grooved Pegboard	Praxis Somatosensory Somatosensory Fine Motor Fine Motor
Visuospatial Functions	Difficulty navigating familiar environment	Clock Drawing Test Judgment of Line Orientation Hooper Visual Organization Test Facial Recognition Test	Planning, construction Visuospatial Perception Visuospatial Integration
Executive Functions	Multi-stage projects are effortful or avoided Poor task persistence Perseverates Double alternating hand movements.	Trail Making Test Stroop Test Controlled Oral Word Association Test (COWAT) Wisconsin Card Sorting Test (WCST) Iowa Gambling Task (IGT)	Set-Shifting Cognitive Inhibition/Processing Speed Strategy Perseveration, Flexibility Reward-based Decision Making
Social Awareness	Impaired recognition of social cues Takes unusual liberties Apathetic Insistent, overbearing	Apathy Evaluation Scale (AES)	

[1] This is not an exhaustive list of neuropsychological functions and measures, but rather a sample of measures that may be used to assess aspects of cognitive function in older adults.

Table 2

Psychotherapies for Depressed Older Adults

Name of Psychotherapy	Target Population	Location of Delivery	Duration	Specific Techniques
Problem Solving Therapy for Executive Dysfunction (PST-ED)[54]	Depressed, non-demented older adults with executive dysfunction	Outpatient setting	12 weekly sessions	Problem solving skills: Problem definition, goal setting, generation of alternative solutions, decision making, planning.
Problem Adaptive Therapy (PATH)[53]	Depressed, disabled older adults with significant cognitive impairment	Patient's home	12 weekly sessions	Problem-solving skills, caregiver involvement, environmental adaptation tools (e.g., notebooks, calendars, pill boxes, alarms, timers, checklists, and step-by-step breakdown of tasks).
Cognitive Behavior Therapy for Mild Dementia (CBT-Mild Dementia)[58]	Depressed older adults with mild dementia	Outpatient setting	16–20 weekly sessions	Cognitive strategies (e.g., examining the evidence, listing pros and cons, cognitive restructuring), behavioral activation, memory aids.
Behavior Therapy – Positive Events (BT-PE)[59]	Depressed older adults with moderate to severe dementia and their caregivers	Outpatient setting	9 weekly sessions	Behavioral strategies (e.g., identifying, planning, and carrying out positive activities as well as identifying and eliminating obstacles).
Behavior Therapy – Problem-solving (BT-PS)[59]	Depressed older adults with moderate to severe dementia and their caregivers	Outpatient setting	9 weekly sessions	Problem-solving skills training to caregivers; education, advice, and support to caregivers.
Interpersonal Psychotherapy for Mild Cognitive Impairment (IPT-CI)[60]	Depressed older adults with mild cognitive impairment	Outpatient setting	12–16 weekly sessions	Interpersonal skills, joint caregiver-patient sessions.
Personalized Adherence Intervention for Depression and COPD (PID-C)[55]	Depressed older adults with COPD	Outpatient setting	9 weekly sessions	Skills to target barriers to adherence (i.e. misconceptions, misunderstanding of recommendations, misattribution of symptoms, stigma, hopelessness, dissatisfaction with treatment experience, logistic barriers).
Ecosystem Focused Therapy (EFT)[57]	Older adults with post-stroke depression	Patient's home	12 weekly sessions	New perspective, adherence enhancement structure, problem solving structure, re-engineering goals and plans of family, coordination of specialized therapists.
Engage[56]	Depressed older adults	Outpatient setting	9 weekly sessions	Reward exposure (action planning to increase rewarding activities). Behavioral techniques targeting barriers (negativity bias, apathy, emotional dysregulation) to reward exposure.