Cognitive rehabilitation therapies for Alzheimer's disease: A review of methods to improve treatment engagement and self-efficacy

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Abstract

Cognitive rehabilitation therapies for Alzheimer's disease (AD) are becoming more readily available to the geriatric population in an attempt to curb the insidious decline in cognitive and functional performance. However, people with AD may have difficulty adhering to these cognitive treatments due to denial of memory deficits, compromised brain systems, cognitive incapacity for self-awareness, general difficulty following through on daily tasks, lack of motivation, hopelessness, and apathy, all of which may be either due to the illness or be secondary to depression. Cognitive rehabilitation training exercises are also labor intensive and, unfortunately, serve as a repeated reminder about the memory impairments and attendant functional consequences. In order for cognitive rehabilitation methods to be effective, patients must be adequately engaged and motivated to not only begin a rehabilitation program but also to remain involved in the intervention until a therapeutic dosage can be attained. We review approaches to cognitive rehabilitation in AD, neuropsychological as well as psychological obstacles to effective treatment in this population, and methods that target adherence to treatment and may therefore be applicable to cognitive rehabilitation therapies for AD. The goal is to stimulate discussion among researchers and clinicians alike on how treatment effects may be mediated by engagement in treatment, and what can be done to enhance patient adherence for cognitive rehabilitation therapies in order to obtain greater cognitive and functional benefits from the treatment itself.

Keywords

cognitive rehabilitation; treatment engagement; adherence; motivation

The overall prevalence of Alzheimer's disease (AD) is rapidly increasing, with an estimated 16 million diagnosed cases projected by the year 2050 (NIH Alzheimer's disease Fact Sheet, 2005). A whole generation of baby boomers are aging and reaching a vulnerable stage where they are susceptible to neurodegenerative disorders. AD is the leading cause of dementia in the general US population (Cummings Jl, 2002, van Dyck *et al.*, 2007) and is often associated with a high risk of comorbid medical and psychiatric disorders, which further strain medical center and family resources due to their high direct and indirect costs (Fillit and Hill, 2004). As health systems prepare to accommodate an influx of dementing older

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adults across the US, it is particularly important to develop effective, targeted treatments to halt or delay the onset of cognitive decline associated with AD. Even if the delay is only temporary, doing so may have a significant positive impact on the high treatment costs associated with AD. Indeed, preventing a 2-point decline on the Mini Mental Status Examination (MMSE) could save a family thousands of dollars annually, while a 2-point increase in MMSE score would save even more (Ernst Rl, 1997).

Medications such as cholinesterase inhibitors and memantine provide limited benefits, but recent evidence suggests that concurrent pharmacologic and behavioral methods may maximize functional benefits for patients suffering from dementia (Buschert *et al.*, 2010, van Dyck, 2004). Cognitive enhancement therapies for early and moderate AD are becoming more readily available to the geriatric population in an attempt to curb the insidious decline in cognitive and functional performance (Cipriani *et al.*, 2006, Farina *et al.*, 2002, Talassi *et al.*, 2007). Cognitive enhancement is a behavioral treatment for cognitive impairment that targets cognitive skills and fosters improvement through the practice of compensatory and/or restorative strategies (Kurtz, 2003, Twamley *et al.*, 2008, Wykes and Spaulding, 2011). These methods entail either learning strategies that minimize cognitive demands (compensation) or repeatedly practicing cognitive skills until premorbid performance levels are reached.

To date, cognitive training has been successfully used to target cognitive impairments in other disorders such as schizophrenia (Fiszdon *et al.*, 2005, Twamley *et al.*, 2012, Wexler and Bell, 2005, Wykes *et al.*, 2011), head injury (Cicerone *et al.*, 2005, Cicerone *et al.*, 2011), stroke (Lincoln *et al.*, 2000, Rohling *et al.*, 2009), and substance abuse (Vocci, 2008). However, the unique circumstances surrounding dementia present distinctive challenges for the effective administration of cognitive enhancement therapies. In this paper, we discuss cognitive enhancement methods that have been studied in AD as well as the obstacles related to the successful delivery of these treatments, and offer therapeutic approaches that have been used successfully in other populations to promote engagement and adherence, which may also improve efficacy and outcome for AD.

Cognitive enhancement in Alzheimer's disease

The core premise of cognitive enhancement therapies for AD is based on neuronal plasticity. Aging causes gradual loss in brain systems including neuromodulatory functioning. However, only recently have we learned that the nervous system has the ability to adjust its structural organization in response to the environment (Mahncke *et al.*, 2006a). The brain has the capability for restructuring itself to adapt to changing circumstances or novel stressors. We know this happens in normal older adults with plasticity-promoting training (Ball et al., 2002, Mahncke *et al.*, 2006b). Training can drive brain plasticity by engaging adults in stimulating cognitive, sensory, and psychomotor activities on a concentrated basis (Olesen, 2004). The training re-engages and fortifies the neuromodulatory systems that control learning, with the goal of increasing the power of cortical representations. Studies indicate that cognitive enhancement therapies can alter brain function at the molecular and synaptic levels, as well as at the neural network level. At the cellular level, this net change in neuronal activity may reflect greater activation of a minority of neurons as a result of the intervention stimulus. In a PET study of 70 patients with mild AD comparing social support, drug therapy, and/or cognitive training, a combination of cognitive training and phosphatidylserine or pyritinol drug therapy was associated with increased brain glucose metabolism in temporal–parietal brain areas during a visual recognition task (Heiss *et al.*, 1994). In a single-blind randomized controlled trial consisting of cognitive rehabilitation (CR) and relaxation therapy versus no treatment in mild AD, Clare et al. (2010) found an increase in blood oxygen level-dependent (BOLD) signals in the CR group in areas forming

part of the network for visual associative encoding and learning (right fusiform face area, right parahippocampal cortex, right temporal parietal junction, right medial prefrontal cortex) while individuals in the control condition showed reduced BOLD activity over time.

Neural activity associated with the performance of a cognitive task might also *decrease* as a result of training, as the response time to accomplish the task decreases with practice and experience, meaning that less neural processing is necessary to perform the exercise (Haier *et al.*, 1992). The neuromodulatory systems commonly impaired in AD are upstream to global cognitive and social deficits. When sensory input is degraded, the brain must adjust by lengthening space and time integration constants in an effort to detect relevant signals. This adaptation comes at a cost: the brain cannot accurately represent details of spatiotemporally complex signals. This can be seen in studies examining the biological mechanisms involved in enhancing cognition in schizophrenia. Deficits in visual processing in psychosis suggest dysfunction even at the earliest stages of cortical processing. As novel visual cognitive activities become more challenging, behavior is adapted in ways that reinforce negative aspects of sensory input (Butler *et al.*, 2005, Johannesen *et al.*, 2008). The targeted neural mechanisms in cognitive training programs for psychosis link functional decreases in brain activity to more efficient information processing. This may also hold true for older adults with memory impairments. A PET study found that elderly patients with mild age-related memory complaints who underwent a 14-day program combining mental stimulation, verbal memory training, physical exercise, stress reduction and a healthy diet demonstrated better verbal fluency but a decrease in activity in the left dorsolateral prefrontal cortex. Patients in the control group who went about their usual daily routine showed no significant change in brain activity or improvement in any cognitive domains. This reduction in the resting activity of the left dorsolateral prefrontal cortex may reflect greater cognitive proficiency of a brain region involved in working memory (Small *et al.*, 2006).

Clare and Woods (2004) provided the first synthesis of cognitive enhancement in AD, and grouped the various treatments into three broad categories: cognitive stimulation, cognitive training, and cognitive rehabilitation. Below, we provide an overview of these three treatment approaches.

Cognitive stimulation

As the name implies, cognitive stimulation entails engaging the patient in discussions about common everyday tasks in an effort to stimulate mental activity (Cotelli *et al.*, 2006, Davis *et al.*, 2001, Tárraga *et al.*, 2006). One cognitive stimulation technique commonly employed is "reality orientation" (Spector *et al.*, 2000). As described by Spector et al. (2003) in their version of cognitive stimulation, a "reality orientation board" is used to display both personal and orientation information (group name, location, time, etc). Specific topics included on the board consist of using money, word games, present day information, and famous faces. The therapy focuses on repeatedly reminding patients of information using themes (such as childhood and food) in order to create continuity between different bits of information (Spector *et al.*, 2010). All sessions allow for the natural process of reminiscence, but also emphasize how the information relates to the current day (Spector *et al.*, 2008). As one might expect, this type of therapy is predominantly geared toward more impaired AD patients who live in residential facilities. In a large, single-blind, randomized comparison in residential or adult day centers, those with moderate AD who received Spector's CST showed better cognition on the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) (Rosen *et al.*, 1984) (F=6.18, p=.014) and MMSE (Folstein *et al.*, 1975) (F=4.14, p=.044) and rated their quality of life more positively on the Quality of Life-Alzheimer's Disease scale (QoL-AD)(Logsdon *et al.*, 1999)(F=4.95, P=.028) than those in the treatment as usual control groups (Spector *et al.*, 2010).

Cognitive training

In contrast to cognitive stimulation, cognitive training (CT) is geared toward patients who have enough cognitive resources for a therapist or a computer program to guide them in scaffolded drill and practice of tasks designed to exercise specific cognitive functions or to work on relatively *intact* cognitive skills in order to support more impaired cognitive skills. CT is based on the premise of neuroplasticity--that practicing an isolated underlying cognitive skill has the potential to improve or at least maintain performance in a particular domain. There have been studies of computer-based cognitive training in AD using software packages that isolate and repeatedly train specific cognitive domains such as divided attention, spatial memory, or object discrimination. Cipriani et al. (2006) and Talassi et al. (2007) both tested a software package called Neuropsychological Training (NPT) that was originally designed for aphasia but modified for brain damage rehabilitation. The goal was to determine if NPT could be further modified for CT in AD by targeting only preserved or mildly impaired cognitive areas to improve memory in dementia. Training consisted of 30–45 minutes sessions, 4 days a week, for 3 weeks. Domain-specific exercises targeted divided attention, object identification, sequential memory, working and spatial memory, visual discrimination (for faces), phonological discrimination and recognition, and verbal comprehension. Talassi and colleagues (2007) found significant improvement in overall cognition (MMSE, p=.002), depression (Geriatric Depression Scale, p=.030), and working memory (Digit span, p=.021) in community dwelling patients with AD when compared against a control that did physical rehabilitation exercises instead of CT. Cipriani and colleagues (2006) found additional gains in executive functioning (Trailmaking Test B, p = .050; verbal fluency, p = .036) suggesting that AD patients can benefit from computer-based CT if the training targets functions that are still relatively well preserved.

One-on-one training approaches to CT have also been used in AD. For example, Clare (2003a) and Moore et al. (2001) have both examined the efficacy of a trained therapist repeatedly practicing with the patient the recall of names, faces, places and events, or repeatedly practicing situation-specific tasks, with the focus of the therapy on rehearsal and high effort. CT has also been combined with motor movements or practicing Activities of Daily Living (ADLs) to increase the procedural associations between learning an activity and remembering the steps involved. For example, patients can choose a particular body movement that matches a name or event to recall (e.g. the movement of throwing a ball can be associated with the name of the therapist). Personal physical gestures along with the information to recall are then repeatedly practiced and rehearsed (Ávila *et al.*, 2004). In a study of 25 patients with moderate dementia vs. age matched controls, Moore et al. (2001) found that 5 weeks of CT that entailed name–face rehearsal and practiced effortful recall of significant information and events in conjunction with pantomiming personal motor movements improved processing speed (Kendrick Digit Copy, t = 2.952, p = .006), depression (Geriatric Depression Scale, t = 2.071, p = .040), and caregiver perceptions of the patient's memory ability (Memory Functional Questionnaire, t = 2.125, p = .040) even a month after the course was completed.

Another variation of CT, Cognitive-Motor Intervention (CMI) (Olazarán *et al.*, 2004), combines practicing ADLs and cognitive exercises with cognitive stimulation techniques such as reality orientation. In an efficacy trial of CMI against a psychosocial support group, patients diagnosed with mild to moderate AD who were on cholinesterase inhibitors were randomized to receive psychosocial support plus CMI or psychosocial support alone. Compared to psychosocial support alone, which was associated with a decline in overall cognitive status, there was immediate improvement in overall cognition on the ADAS-Cog in the CMI + psychosocial support group after just 1 month of training (Z = −1.95, p = 0.050). This benefit for the CMI + psychosocial support group was maintained throughout

the course of the intervention with improved quality of life reported at the end of treatment (p=.005).

Cognitive rehabilitation

Cognitive rehabilitation (CR) refers to a comprehensive cognitive enhancement program, wherein multiple training approaches are offered in a rehabilitation milieu setting. This model of inclusive treatment encompasses cognitive stimulation, cognitive training and other approaches, in the context of a biopsychosocial, individualized approach to understanding dementia (Clare *et al.*, 2010). In CR, all facets of neuropsychological deficits are considered (and addressed) in the context of behavior and social functioning (Wilson, 2002). A good example of the use of CR for individuals with AD is a therapy studied by Loewenstein and colleagues (2004). In this particular application, CR is administered individually and consists of (a) cognitive stimulation by practicing time-and-place orientation through in-session rehearsal, (b) computer-based drill and practice cognitive training for sustained attention and visual motor processing speed (c) bridging cognitive and procedural motor activation by learning and practicing manipulation of everyday objects, and (d) training and rehearsing ADLs such as making change when shopping, balancing a checkbook by hand or calculator, or paying utility bills. In a rigorous randomized controlled trial against generic mental stimulation provided by computer puzzle games, Loewenstein and colleagues found that CR produced improvements in orientation (Group $\times$ Time Interaction, p=.006) and learning and recalling faces and names even at 3-month follow-up (Group $\times$ Time Interaction, p=<.001–.004). Only informants of patients in the CR condition noted a significant improvement in memory function on the Informant Questionnaire of the Cognitive Decline in the Elderly scale (Group $\times$ Time Interaction, p=.033). Importantly, the CR group made meaningful gains on an untrained functional task (Making-Change-For-A-Purchase Task, Group $\times$ Time Interaction, p=.006). These results suggest that CR programs in AD should target the training of applied real-world tasks rather than merely targeting broad theoretical cognitive domains (Loewenstein *et al.*, 2004).

As may be clear from the above description, CR does not merely target specific cognitive abilities, but offers a model of treating the cognitive decline on the basis of current behavioral and social disability. Cognitive gains are considered in the context of the interaction between the patient and the environment. In this respect, CR in AD does not only include models that emphasize restoring or halting cognitive deficits, but finding, learning, and practicing methods of compensating so that cognitive demands are minimized. This type of compensation can range from learning and practicing how to arrange finances in such a way that the monthly utility bills are easier to remember and complete, to learning how to use calendars or computer and paper-and-pencil aids to organize and recall important information such as medication. Compensatory methods do not merely involve memory aids or environmental prosthetic supports. Patients are trained in the use of external supports through repeated practice, along with verbal instructions and physical demonstrations, so they can learn and master compensatory techniques that can then be applied to other situations.

While the use of multiple training approaches is a definite strength of CR, it also makes it difficult to determine the efficacy of its various subcomponents. To date, only two meta-analyses (Clare *et al.*, 2003b, Sitzer *et al.*, 2006) have examined the efficacy of cognitive rehabilitation. Unfortunately, both meta-analyses grouped the various types of methods (cognitive stimulation, cognitive training) under a single rubric, and did not allow for a comparison between specific methods. Although research to date has been hampered by small, underpowered studies and a lack of randomized controlled trials, the results of these meta-analyses have nevertheless been illuminating. It appears that, broadly, CR is associated with medium effects sizes on cognitive function (ES=.540) and performance-based ADLs

(ES=.690) but only a small effect on informant reports of functional ability (ES=.110) (Clare and Woods, 2004, Sitzer *et al.*, 2006). While very rigorous comparisons of CR to active control treatments (e.g. general mental stimulation) show no effects on tests of memory (ES= −.050 to .070) or on the MMSE (ES= −.060) (Clare and Woods, 2004), some have argued that the active control treatments are in fact a form of CR, which would suggest that both CR and general mental stimulation show some positive effects on cognitive function. Cognitive deterioration in AD has yet to be addressed even with intense and long-term CR programs; however, deterioration is greater and progresses faster in patients not receiving CR at all (Buschert *et al.*, 2010).

Since 2006, there have been few randomized controlled trials of CR for AD, with the research focus shifting to preventing AD at prodromal stages of preclinical decline, i.e., Mild Cognitive Impairment (MCI). Epidemiological and clinical studies suggest that mental activity levels may delay the onset of dementia by enhancing neuronal plasticity. In healthy older adults, there is a substantial effect size for CR compared with wait-and-see control conditions (weighted mean difference = 1.07) (Valenzuela and Sachdev, 2009). However, CR for mitigating the cognitive deterioration due to AD is hampered by a number of unique treatment and disease factors, as discussed below.

Obstacles to cognitive rehabilitation in Alzheimer's disease

Unlike CR for conditions such as schizophrenia or TBI where the impairment is relatively static, the CR program for dementia must take into account a progressively declining mental status, compromised brain systems involved in understanding or even being aware of the illness, and the increasingly apparent relationship between geriatric depression and dementia. Although mitigating the severity of neurodegenerative decline is a monumental task, slowing down cognitive decline to allow for even a few more months of independent function can significantly impact patients' quality of life by delaying the need for more intense and confining levels of care. However, there are a number of neuropsychological and psychological obstacles when attempting to engage patients with AD in CR (Figure 1).

Cognitive deficits

The first and foremost obstacle is the most evident and may be the most pertinent. The insidious loss of cognitive capacity, specifically memory, language, and then executive skills needed to perform daily life tasks, renders the patient with declining resources to benefit from CR. The beneficial effects of CR are directly related to this degree of cognitive reserve. Individuals deemed to have greater reserves, either through education or lifelong mentally demanding professions or lifestyles, have a reduced risk of developing dementia (Stern, 2006) and may benefit more from cognitive therapies (Scarmeas and Stern, 2004). The significant impairments in episodic memory make it difficult to take in new information, which in essence, is the principal goal of CR – to learn new or more adaptive cognitive skills. Memory difficulties can also curtail self-efficacy, which can then lead to social withdrawal from activities and a complex relationship with depression (discussed below), thereby exacerbating the diminishing capacity even further (Clare and Woods, 2004). Indeed, the distinct cognitive deficits of AD make it difficult to recall CR instructions, learn about the utility or value of the treatment, retain new strategies, and translate cognitive gains into real-world abilities. As the disease progresses, the varying level of cognitive functioning further complicates the treatment picture. For example, patients with advanced AD symptoms may receive fewer benefits from CR that targets specific cognitive domains than patients in the earlier stages. By contrast, cognitive stimulation and intervention strategies that support performance of daily activities might provide more benefits to patients further along in the disease (Buschert *et al.*, 2010). Within this profile of retained and compromised abilities, given appropriate conditions and

therapeutic modifications to optimize treatment engagement and CR, people with dementia still have the ability to learn and retain useful information and skills despite their memory difficulties.

Denial/anosognosia

Quite commonly, patients deny the presence or severity of cognitive and functional impairments, despite palpable evidence to the contrary (Clare *et al.*, 2004, Smith *et al.*, 2000). Anosognosia has been described as a lack of awareness or insight into the illness, which may represent a defense mechanism, an impairment in the cognitive processes that support insight, or both. Although theoretical explanations of the construct of denial/ anosognosia (or unawareness) remain speculative, empirical studies on the discrepancy between impairments reported by the individual with dementia and those reported by an informant (often a spouse) have begun to clarify aspects of unawareness in dementia (Hardy *et al.*, 2006). For a comprehensive review of denial and anosognosia in AD, please see Ecklund-Johnson and Torres (2005). Below, we explore both the psychological concept of denial and the possible brain systems involved in anosagnosia.

While the degree of denial is not significantly related to severity of symptoms or decline in ADLs, it is significantly (negatively) correlated with levels of depression (Feher *et al.*, 1991). Macquarrie (2005) offers a unique perspective on how acknowledgement of the disease (and its eventual progression) is intertwined with paradoxical resistance to its inevitable final outcome. This resistance is expressed through denial and minimization as the patient attempts to maintain a sense of organization and competence when faced with a terminal illness. In an early study using the patient-informant discrepancy to operationalize unawareness of deficits, Reisberg (1985) found that while patients with AD appeared to underestimate their own deficits, they were generally correct in their assessment of their spouses' memory abilities. This indicated a defensive denial because patients with AD appeared to maintain the ability to report accurately on someone else's memory functioning but overestimated their own memory abilities. This denial may be at the core of non-adherence to CR and other treatments, and the relationship between denial and depression bears on this matter. When faced with advancing decline and life's finitude, patients recall events and achievements where they experienced competency and a sense of control. In stark contrast to this, their present lack of control over their cognitive abilities and functioning produces a profound loss of self-efficacy and anticipation for the future. In this sense, poor treatment adherence is completely understandable – why agree to engage in hours of a treatment that will not reverse the illness, especially when the number of hours left is now painfully obvious? Depression sets in and futility overwhelms any sense of urgency to seek treatment.

In contrast, McGlynn and Kaszniak (1991) proposed that impaired awareness results from dysfunction of frontal lobe brain systems necessary for self-monitoring rather than defensive denial. Similar to Reisberg (1985), they also found that patients with AD tend to overestimate their memory abilities, particularly on cognitive tasks in which their performance has changed most dramatically as a consequence of dementia (delayed verbal recall, visual memory, working memory). However, if a defense mechanism of denial was the major factor accounting for the apparent unawareness, one would expect the denial to be most evident early in the disease when patients are beginning to recognize changes in their functioning but are not yet prepared to tackle the somber consequences of those changes. McGlynn and Kaszniak (1991) found just the opposite--patients were more likely to accurately gauge their memory difficulties at earlier stages of the disease process than at later stages. They were the first to suggest that marked neurocognitive decline associated with the disease interferes with the ability to correctly monitor changes in cognitive functioning *over time*.

The frontal dysfunction hypothesis in anosognosia continues to be a prevailing topic, given the commonality between AD and frontal dementia as both diseases progress (Seelaar *et al.*, 2011). The full range of unawareness between complete awareness of deficit onset/severity and total anosognosia may reflect damage to specific brain systems that are crucial for self-awareness or metacognition (Michon *et al.*, 1994). The frontal hypoperfusion associated with reduced awareness of deficits in brain injury has led some to suggest the existence of a hypofunctioning prefrontal pathway involving the right dorsolateral prefrontal cortex, inferior parietal lobe, anterior cingulate gyri and limbic structures in dementia (Amanzio *et al.*, 2011). This network plays an important role in response inhibition, and AD patients who are unaware of their deficits exhibit impaired performance in response inhibition tasks. This was the case in the most recent neuroimaging trial by Amanzio and colleagues (2011). Unaware AD patients showed reduced task-sensitive activity in the right anterior cingulate area and in the rostral prefrontal cortex while performing a go-no go training task. Unaware patients also showed reduced activity in the right post-central gyrus, in the associative cortical areas such as the right parietotemporal–occipital junction and the left temporal gyrus, in the striatum and in the cerebellum. These findings suggest that the unawareness of deficits in AD may be associated with reduced functional recruitment of the cingulofrontal and parietotemporal regions (Amanzio *et al.*, 2011).

Operationalizing awareness and the influences of cognitive deterioration and anosognosia plays an important role in engaging patients in a labor-intensive treatment such as CR. Earlier views did not perceive denial or unawareness as necessarily unconstructive or harmful, just as a mechanism to adapt or cope, especially in the early stages of illness (Weinstein, 1991). However, more evidence has come to light in brain injury and dementia that denial may interfere with progress in CR. The implications for CR are significant in relation to AD, as recent attempts to develop CR approaches have indicated that higher levels of awareness of difficulties appear to be associated with better outcome. For example, Koltai (2001) studied CR in 24 patients with mild to moderate AD and found that higher levels of awareness were strongly predictive of greater gains in perceived memory functioning. That is, all patients with intact awareness reported fewer memory failures following CR on the Everyday Memory Questionnaire (Sunderland *et al.*, 1983) compared to patients without awareness (p=.028). In contrast, informants perceived greater gains among treatment subjects relative to controls independent of insight status. These results reinforce the notion that awareness may well be an important variable that moderates CR outcome.

Depression/hopelessness

Depression is commonly reported in people with AD, from the early to advanced stages of cognitive and functional decline (Fry, 1984, Panza *et al.*, 2010). The importance of considering depression is threefold: (a) depression can be a significant confounding factor in any type of CR program because it exacerbates or may be the cause of cognitive impairments rather than AD-related deterioration, (b) depression itself appears to be a risk factor for AD, and (c) regardless of etiology, depression can lead to a downward spiral of hopelessness. The cognitive impairments associated with depression have been extensively reviewed in the last decade, with an increasing awareness of the extent and severity of cognitive deficits and the difficulties associated with conducting CR for patients with depression (Clare *et al.*, 2003a, Elgamal *et al.*, 2007, Wilson, 2002). Here we focus more on how depression may be related to AD and the unique hurdles presented by distinct feelings of hopelessness in late-life depression.

Initially, meta-analyses focused on how dementia served as a risk factor for depression. In old age, individuals with dementia had both significantly higher prevalence and incidence rates of depression than those without dementia (Huang *et al.*, 2011). Very recently,

following intense scrutiny of methods to reduce common and treatable risk factors for dementia (such as diabetes, hypertension, obesity, smoking, depression, cognitive inactivity or low educational attainment, physical inactivity), researchers found that about 10% of diagnosed AD cases could be directly attributable to depression (Barnes and Yaffe, 2011). Two large meta-analyses have found depression to be a reliable risk factor for MCI and AD. In 12 different cohort studies that followed patients without dementia or MCI at baseline, Gao et al. (2012) showed that older patients with depression had a significantly higher incidence of MCI (RR: 1.97, 95% CI: 1.53– 2.54) and AD (RR: 1.66, 95 CI%:1.29–2.14) than those without depression. Steenland et al. (2012) separately analyzed the role of depression in the progression from either normal cognition to MCI or from MCI to AD. Tellingly, those reporting depression had an increased risk for progression from normal to MCI (RR = 2.35; 95% CI 1.93–3.08). Normal subjects, identified as depressed at first visit but subsequently improved were found to have an increased but lower risk of progression to MCI (RR = 1.40; 95% CI 1.01–1.95). Those reporting depression had a modest increased risk of progression from MCI to AD (RR = 1.21; 95% CI 1.00–1.46).

Furthermore, research that suggests that early-onset or chronic depression that is untreated or recurrent may be associated with volume loss in the hippocampus (Potter and Steffens, 2007) and possibly contributes to dysfunction of the hypothalamic-pituitary-adrenalstress axis (Sapolsky, 2001). One particular neuroimaging study by Bell-McGinty et al. (2002) analyzed scans from 30 depressed patients 59 to 78 years old and 47 nondepressed comparison subjects. They found that depressed patients had smaller right hippocampal-entorhinal volume, providing additional evidence of structural brain abnormalities in geriatric depression leading to neurodegenerative diseases. Behaviorally, these deficits in a number of prefrontally mediated cognitive processes, such as selective attention, response inhibition, planning, and performance monitoring overlap considerably with AD and are associated with worse acute and long-term treatment response and greater functional disability in depression. This highlights the importance of always considering depression in CR or any type of treatment for AD, as researchers try to identify effective strategies to delay the onset or slow the progress of dementia. Both depression and cognitive deterioration seem to have overlapping neuropathology and severe consequences, including diminished quality of life, functional decline, and disengagement from treatment services such as CR.

Depression in AD can also be unique in that it is primarily derived from a sense of hopelessness. The anxiety, blunted affect, psychomotor retardation, and neurovegetative symptoms (e.g., sleep and appetite disturbance) are coupled with a heightened awareness of mortality, leading many to endorse the belief that "life was not worth living" (Harwood and Sultzer, 2002, Lyketsos and Olin, 2002). Studies have alarmingly reported 5.4% to 9.7% of patients with AD report hopeless ideation or the thought that life is not worth living (Harwood and Sultzer, 2002). In AD, hopelessness commonly manifests itself through poor self-esteem, anticipation of the worst in everyday situations, and little or no expectations of success (Alexopoulos *et al.*, 1988b). Feelings of hopelessness, pessimistic thoughts, expectation of failure, and low self-efficacy are already evident in a significant percentage of patients with mild cognitive impairment and are reported more frequently than other common depressive symptoms, such as guilt or suicidal ideation (Lopez *et al.*, 2005, Robert *et al.*, 2006). Such hopelessness and feelings of failure are a reaction to a belief that one's quality of life has essentially ended, which in turn leads to catastrophizing rather than adapting to the disability. This spiral of decline, intertwined with depression and negative expectations, has been implicated with caregiver distress and heightened risk for nursing home care (Haupt and Kurz, 1993).

Defeatist beliefs

Defeatist beliefs are dysfunctional schemas that are automatically generated in response to feelings of hopelessness (e.g. "If I can't remember this name, I am a complete failure and there is no use doing the rest of the training"; "I won't be able to do this well, so why bother?"). These dysfunctional thoughts lead individuals to assume the worst outcome and contribute to a poor sense of self-competence that influences both mood and behavior, and thereby worsens already declining cognitive and functional abilities by preventing people from using even their more intact skills and abilities (Starkstein *et al.*, 2005). Low self-efficacy and expectations of failure already play a fundamental role in governing goal-directed, task-centered behavior. Low self-efficacy is characterized by defeatist beliefs and refers to a lack of conviction in the ability to produce desirable consequences on a given task (Bandura, 2006). Defeatist beliefs, such as those that are common among AD patients who experience hopelessness, may reduce the likelihood of engaging in new treatments, the probability of continuing the treatment as its level of difficulty increases, and the degree to which treatment gains are retained. Bandura concluded that a high level of self-efficacy is necessary in order to overcome challenges and failures. One could conceive that for patients diagnosed with AD, to whom simple, daily tasks often seem insurmountable, such a level of assurance in one's abilities and perseverance through adversity may seem significantly less attainable.

Bandura's theory of perceived self-efficacy (Bandura, 1993, 2006) could readily be applied to the task-focused nature of CR treatment for AD, possibly unveiling an essential component of patient response to, and extent of benefit from, such treatment programs. When considering factors that may influence patient response to CR programs within this population, the frequently reported feelings of hopelessness and defeatist beliefs (as manifested by low expectations of success) can have an adverse impact on the efficacy of CR, as these types of labor-intensive treatments require a high degree of task engagement. AD patients may be less inclined to actively engage in CR due to their beliefs that failure is inevitable. Defeatist beliefs may alter help-seeking behavior and perpetuate cognitive dysfunction by encouraging avoidance of potentially challenging treatment tasks. A lack of effort toward cognitive treatment can hinder not only performance on the specific training tasks, but more importantly, the ultimate outcome of treatment. Defeatist beliefs and efficacy expectations are known to play a crucial role in treating cognitive and functional impairments in schizophrenia (Choi *et al.*, 2010, Granholm *et al.*, 2009, Grant and Beck, 2009, Horan *et al.*, 2010). For example, in a study of cognitive enhancement with patients with schizophrenia, Choi et al. (2010) showed that baseline expectation of success was a strong predictor of persistence of learning effects on a computer-based learning task. This highlights the vital nature of performance beliefs on learning retention. In AD, our group has also found that higher levels of hopelessness and lower expectations of success at baseline were correlated with less improvement in memory after CR. Furthermore, baseline expectation of success was a significant predictor of cognitive outcome at follow-up, above and beyond the effects of baseline memory ability, overall dementia symptoms, and depressive symptoms. In sum, it appears that hopelessness and defeatist beliefs are significant limiting factors for the efficacy of CR for AD, and negative outcomes in CR may be linked with expectations and beliefs of failure.

Task value

Another factor that contributes to poor treatment engagement is a person's understanding of the purpose behind, and the value of, specific training tasks or treatment programs (Wigfield and Eccles, 2000). While some CR tasks have high face validity (e.g. practice remembering names), for many other tasks (e.g. sustained attention tasks that entail tracking a target across the screen), it may not be readily apparent to the patient how repeated practice may

lead to important cognitive or functional improvements. In cases such as this, it is imperative that adequate justification for specific tasks is provided to the patients (perhaps repeatedly). A simple explanation that practicing tracking a target across the screen can improve concentration, and that concentration is the first step in remembering important details, can make the difference between the patient seeing the task as irrelevant or of high value to his or her goals. Without an understanding of the importance of specific training tasks, patients tend to put less effort into training and make more errors, which can reinforce defeatist beliefs. In contrast, seeing a training task as personally meaningful and related to one's goals can lead to higher internal motivation to continue training and better task engagement, even as the training difficulty increases.

For rehabilitation methods to be effective, patients must be adequately motivated to participate consistently in order to achieve adequate treatment intensity. Below, we discuss CR therapies and techniques that address some of these obstacles to treatment engagement.

Strategies to improve treatment adherence

Cognitive rehabilitation for AD usually involves not only training for the patient, but also education with and engagement of the family/caregiver support systems. It is well known that involving these support systems in therapy plays a crucial role in enhancing the patient's engagement and the efficacy of the intervention, and readers interested in further information on this topic are referred to Martire et al (2004), Mittelman et al. (2004), Schulz and Martire (2004), and Woods (2001). We limit the current review specifically to strategies that can be applied to the patient and/or the CR program.

Cognitive Vitality Training (CVT)

Patients recently diagnosed with AD (and their caregivers) experience a tremendous loss of control in their lives, and therapies that strive to reintroduce elements of control and self-efficacy may offer psychological as well as neuropsychological benefits. For this reason, cognitive interventions that not only target the failing neurocognitive domains through cognitive exercises but also enhance understanding and motivation for treatment may be particularly effective. The premise underlying CVT is that in order for a demanding cognitive rehabilitation treatment to be engaging and effective, the patient's feeling of self-competence and self-efficacy must be enhanced by directly targeting hopelessness and defeatist beliefs. This is done by embedding computer-based memory training in a motivational milieu. CVT's "Mental Vitality" program consists of: a rigorous neuroscience-based computerized cognitive training package (Posit Science BrainFitness) (Mahncke *et al.*, 2006a); weekly Cognitive Behavioral Therapy (CBT) sessions targeting feelings of hopelessness and low expectations of success about the computerized cognitive training, active participation from caregivers, and a motivational milieu that emphasizes increasing enjoyment of the training experience, understanding the value of training tasks, and allowing for patient input about how the training progresses. The training is described as one focused on "exercising mental skills" or "optimizing mental acuity" rather than "remediating deficits."

The motivational milieu is specifically intended to increase treatment intensity and adherence to treatment by enhancing intrinsic motivation and empowering people to be actively involved in treatment. The milieu is based on the theoretical framework of other treatment programs where adherence is also a foremost concern: motivation for chronic pain management (Kerns and Habib, 2004) and engaging patients with schizophrenia in psychiatric rehabilitation (Medalia and Freilich, 2008). Both methods empower patients to take control over their treatment by offering a wide range of training menu choices,

individualizing the training plan and goals, personalizing the training activities, and involving family and caregivers in all phases of treatment planning.

Staff who facilitate the computerized memory training that is provided as part of CVT encourage the patients' self-efficacy by providing personalized and tailored instructions and feedback. Patients are allowed to contextualize and personalize incidental features of the training curriculum and the treatment goals (i.e. "I am working on the exercises to get my driver's license back"), and are offered choices of when and how often to do the lessons (i.e. "My goal is to get back to working in my perennial garden and I choose to come in on Monday at 2pm and Thursday at 8am to work on these exercises"). In addition, CVT is also designed to engage the primary caregiver to be actively involved in the program by both participating in the feedback and information sessions, as well as participating in several computer-based exercises along with the patient. CVT is specifically designed to promote patient autonomy (thereby increasing self-efficacy and decreasing helplessness) by allowing them to choose and plan their own treatment.

While the above treatment techniques serve to enhance engagement in the CVT computer-based training exercises, patients may still struggle with continuing in treatment, as impaired performance on training tasks serves as a constant reminder of cognitive decline. This can lead to strain and frustration for both the patient and the caregiver, and can create feelings of hopelessness and low self-efficacy for the training. For this reason, CBT directly targeting dysfunctional and defeatist beliefs about the computerized training is incorporated into CVT. The weekly CBT sessions are conducted jointly with computerized training and focus on (a) mindfulness of dysfunctional schemas - answering automatic thoughts and reconstructing views of the self/environment/AD, (b) identifying and modifying self-defeating thoughts (e.g. Because I can't get this correct, it's hopeless to try any more), (c) emotions that may enhance or interfere with training exercises, and (d) accepting both current accomplishments as well as limitations (Lysaker *et al.*, 2009).

Initial research on CVT appears promising. In a comparison of cognitive training conducted within CVT (n=39) versus the same cognitive training alone (n=30) in early-to-moderate AD patients on cholinesterase inhibitors, those enrolled in CVT for 4 months had better objective memory performance as compared to those enrolled in cognitive training alone for the same dosage. Patients in CVT also reported less severe depressive symptoms on the Cornell Scale for Depression in Dementia (Alexopoulos *et al.*, 1988a) (p=.038) and better quality of life on the Quality of Life-Alzheimer's Disease scale (Logsdon *et al.*, 2002) (p=.041), while their caregivers reported less overall severe depressive symptoms on the Beck Depression Inventory-II (Beck *et al.*, 1996) (p=.026) (Choi, J., Kirwin, P., van Dyck, C.H., Fiszdon, J.M., Bell, M.D. Cognitive vitality training for dementia. Manuscript submitted for publication). Importantly, the CVT group had better attendance over the course of the treatment phase (82%) compared to the cognitive training alone group (69%). No improvements were seen in ADLs in either group. These findings suggest that CT provided in the context of a therapeutic environment, designed specifically to improve self-efficacy and motivation, may be more effective in improving memory and quality of life than CT training alone. These findings also suggest that treatments that enhance self-efficacy may lead to greater motivation for treatment, and possibly, more receptiveness to undertake a difficult intervention such as CR.

Compensatory Cognitive Training

As its name suggests, Compensatory Cognitive Training (CCT) is an approach that relies on training in compensatory cognitive strategies to improve cognition and functioning. CCT emphasizes training in prospective memory, attention, learning/memory, and executive functioning, and has been applied to several populations, including psychosis (Twamley *et*

al., 2012), traumatic brain injury (Huckans *et al.*, 2010), and mild cognitive impairment. CCT is a 10–12 session, weekly therapy that can be delivered individually or in small groups. The treatment manual used by the therapist is also given to clients as a workbook in order to reduce memory demands. Strategies are taught and practiced, and application of the strategies to everyday tasks is discussed and planned. Both internal (e.g., categorizing and visual imagery) and external strategies (e.g., calendars and reminding systems) are included.

There are several aspects of CCT that were designed specifically to enhance motivation and treatment engagement, and that could be applicable to the AD population. First, the treatment is called a "class" to reduce the potential stigma of "therapy" and to emphasize the focus on learning new skills or honing existing skills, rather than discussing problems and deficits. Second, the strategies taught are presented as things that many successful people do to function at their best; thus, the use of cognitive strategies is normalized. Third, family members are invited to accompany clients in order to provide psychoeducation to the caregivers and to teach them the strategies to they can then reinforce strategy use at home and in the community. This is another way of showing that normal people can benefit from strategy use. Fourth, at the beginning of treatment, each individual's functional goals are elicited (e.g., "remember to do things at home to improve relationship with spouse"; "engage in productive activity so I can feel useful"; "remember to take medications so I will stay healthy"). These are then revisited with each cognitive domain addressed (prospective memory, attention, learning/memory, and executive functioning), and the therapist provides overt linkages between the strategies being taught and the functional goals of the individual. This practice serves to individualize the treatment to the client's needs, even in the context of a manualized intervention. Fifth, CCT explicitly addresses attention as a requirement for learning, and learning as a requirement for memory. Because so many clients (regardless of diagnosis) identify memory as a problem, incorporating strategies to improve attention and learning in order to ultimately improve memory has face value. Sixth, CCT emphasizes gradually building mastery by starting off with easier strategies and building to more complicated ones. This way, clients have early mastery experiences that build their confidence and willingness to continue the treatment. Finally, the exercises designed for practicing each strategy were designed to be fun and game-like, and clients are given choices about which examples to use in their practice, in order to increase engagement.

Initial research results indicate that CCT has the potential to improve cognitive test performance, self-reported cognitive problems, cognitively-mediated functional abilities, psychiatric symptoms, and quality of life (Huckans *et al.*, 2010, Twamley *et al.*, 2012). These results suggest that even a brief treatment focusing on compensatory strategies without extensive drills and practice can have effects on both cognition and more distal functional outcomes that are important to clients and their families.

Motivational interviewing

Another approach that has been used successfully to increase treatment adherence is motivational interviewing (MI)(Miller and Rose, 2009, Suarez, 2006). MI is defined as "a collaborative, person-centered form of guiding, to elicit and strengthen motivation for change" (Miller and Rollnick, 2009). Four basic principles guide MI: expressing empathy, developing discrepancy, rolling with resistance/avoiding direct confrontation, and supporting self-efficacy. In general, MI consists of two phases: building motivation for change, and strengthening commitment to change. Specific strategies used in the first phase include asking open-ended questions, reflective listening, affirming the client, providing personal feedback regarding the problem area, using a decisional balance activity to elicit pros and cons of change, eliciting patient statements that favor change (called "change talk), and summarizing material discussed. Strategies common to the second phase of MI include: recognizing a patient's readiness for change, securing a commitment to a specific change

goal, and activating the patient's readiness for change by collaboratively developing a plan to achieve the change. MI normally is a brief intervention delivered in one or two sessions.

While originally developed to facilitate motivation for behavior change in individuals with primary substance use disorders, MI has since been adapted to address a number of different behavioral targets (e.g. treatment adherence, diet, exercise, risky behaviors, gambling, parenting practices, chronic medical conditions). MI has consistent evidence of efficacy across these numerous applications, with a wide range of patient populations (adolescents, adults, psychiatric), including patients who have psychotic illnesses, and specifically for increasing patient engagement in the treatment process. Moreover, the effects of MI in improving targeted outcomes have been shown to be maintained or increased over time when delivered at the beginning of a standard or specified treatment program, with effect sizes hovering in the medium range (Haupt and Kurz, 1993). MI is a treatment that can be successfully taught to medical residents and community based clinicians (Woods, 2001), and has been shown to be effective in real-world community treatment program settings (Schulz and Martire, 2004). While much research has been conducted to evaluate MI, the efficacy of MI in engaging patients with AD in cognitive rehabilitation has not been evaluated to date. Specifically, it is not known whether the degree of cognitive impairments might moderate the efficacy of MI, an approach that likely requires a threshold level of cognitive functioning in that it requires patients to self-reflect, cognitively track what therapists ask or say, appraise the consequences of problem behaviors, and hold in working memory the combined and competing motivations for change. Although individuals with more severe cognitive impairments may be limited in their ability to fully explore the functional consequences of treatment engagement, it may also be that these individuals benefit more from motivational interviewing, in that it provides a guiding structure of discovery, reflection, and evaluation necessary to promote readiness for change.

Errorless learning

Errorless learning has been successfully used in a number of populations, including individuals with learning disabilities (Cockburn and Keene, 2001), autism (Dalla Barba *et al.*, 1995), head injury (Martire *et al.*, 2004, Mittelman *et al.*, 2004), and schizophrenia (Kern *et al.*, 2005). It has also been widely used in individuals with AD as a method of teaching ADLs (Bottino *et al.*, 2005, Clare and Jones, 2008) and memory training such as pairing names with faces (Clare *et al.*, 1999). As the name implies, EL is a procedure designed to teach skills or content in a manner that reduces or eliminates learning errors, or the incorrect pairing of information. By avoiding learning errors, strong associative connections are formed for correct skill sequences. Initially, EL training is highly scaffolded and many cues and prompts are provided to encourage successful learning and recall of training information. Over time, as these associations strengthen, environmental cues may be removed. For example, when teaching a person the steps of making scrambled eggs, the training environment may initially be set up in a way to prompt each of the steps (e.g. having cooking oil right next to frying pan, having only 3 eggs in the container, using a timer to cue when the eggs are done, etc), and as these sequences of actions become more automatic and implicit, the environmental cues may be slowly removed.

This type of training is in direct contrast to certain CT approaches wherein task difficulty is constantly increased until the patient begins to make errors, and may be particularly helpful for individuals with high anxiety levels or severe cognitive impairments. In the case of AD, where explicit memory is impaired and learning relies on the relatively intact implicit learning processes, allowing patients to make errors is particularly counterproductive because AD patients are unlikely to remember what led to an error and what should be avoided in the future, and because commission of errors interferes with the implicit learning process that is emphasized in CR for AD (Derouesné *et al.*, 1999). Additionally, the

experience of making repeated mistakes can result in anxiety and defeatist beliefs, which in turn lead to more errors, frustration, and eventual disengagement from the treatment, whereas EL can build task mastery and willingness to continue to engage in treatment.

Conclusion

In summary, CR for AD should consider all facets of neuropsychological deficits in the context of behavior and social functioning. Engaging patients with AD in cognitive enhancing therapies is particularly difficult because of the progressive nature of the illness. Specific obstacles to successful treatment engagement include lack of insight, depression, hopelessness and defeatist beliefs. Several treatment approaches exist, however, that address some or all of these issues and increase motivation for engaging in rehabilitation. By avoiding learning errors during the training procedures, more robust connections can be developed for correct cognitive skills. As demonstrated by CVT, discrete sessions that instill motivation for CR exercises and strengthen commitment to CR can help clinicians address resistance or avoidance of the rigorous training exercises. Classes that teach and practice implicit methods of compensating so that cognitive lessons are considered a part of normal life while cognitive demands and stigma are minimized can help build experiences of mastery and improve the inclination to continue treatment until the end. Therapeutic milieus that directly target negative expectations and offer individuals more control of their treatment planning and a sense of autonomy can enhance memory training and ease the depression experienced by the patients and their caregivers.

The future of CR in AD lies not only in developing efficacious training paradigms based in neuroscience, but also in how such treatments can be implemented within the context of the immense psychological toll of a dementia diagnosis. As the disease progresses, there are fewer cognitive resources for CR to exploit and less motivation to devote many hours to a labor intensive intervention, albeit even one that may offer some improvement in functioning. Neurocognitive deficits are just one part of the rehabilitation model (Clare et al., 2010), and CR cannot be maximized without understanding and tackling the limiting factors of how AD impacts a person's sense of self and emotional well-being. CR treatments are promising, but the therapy needs to be a more viable option for those who need it. The success of CR seems interweaved with strategies to target the unique problems of AD that impact on adherence, drawing from strategies discussed here that show initial efficacy, as well as developing new methods of treatment engagement.

Acknowledgments

References

Alexopoulos G, Abrams R, Young R, Shamoian C. Cornell Scale for Depression in Dementia. Biological Psychiatry. 1988a; 23:271–284. [PubMed: 3337862]

Alexopoulos GS, Abrams RC, Young RC, Shamoian CA. Cornell scale for depression in dementia. Biological Psychiatry. 1988b; 23:271–284. [PubMed: 3337862]

Amanzio M, Torta DME, Sacco K, Cauda F, D'Agata F, Duca S, Leotta D, Palermo S, Geminiani GC. Unawareness of deficits in Alzheimer's disease: role of the cingulate cortex. Brain. 2011; 134:1061–1076. [PubMed: 21385751]

Avila R, Bottino CMC, Carvalho IAM, Santos CB, Seral C, Miotto EC. Neuropsychological rehabilitation of memory deficits and activities of daily living in patients with Alzheimer's disease:

a pilot study. Brazilian Journal of Medical and Biological Research. 2004; 37:1721–1729. [PubMed: 15517089]

Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. JAMA. 2002; 288:2271–2281. [PubMed: 12425704]

Bandura A. Perceived Self-Efficacy in Cognitive Development and Functioning. Educational Psychologist. 1993; 28:117–148.

Bandura A. Going global with social cognitive theory: From prospect to paydirt. Applied psychology: New frontiers and rewarding careers. 2006:53–79.

Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. The Lancet Neurology. 2011; 10:819–828.

Beck, AT.; Steer, RA.; Brown, GK. Manual for the Beck depression inventory-II. Vol. 1. San Antonio, TX: Psychological Corporation; 1996. p. 82

Bell-McGinty S, Butters MA, Meltzer CC, Greer PJ, Reynolds CF, Becker JT. Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. American Journal of Psychiatry. 2002; 159:1424–1427. [PubMed: 12153839]

Bottino CM, Carvalho IA, Alvarez AMM, Avila R, Zukauskas PR, Bustamante SE, Andrade FC, Hototian SR, Saffi F, Camargo CH. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. Clinical Rehabilitation. 2005; 19:861–869. [PubMed: 16323385]

Buschert V, Bokde ALW, Hampel H. Cognitive intervention in Alzheimer disease. Nat Rev Neurol. 2010; 6:508–517. [PubMed: 20717104]

Butler PD, Zemon V, Schechter I, Saperstein A, Hoptman MJ, Lim K, Revheim N, Silipo G, Javitt DC. Early-stage visual processing and cortical amplification deficits in schizophrenia. Archives of general psychiatry. 2005; 62:495. [PubMed: 15867102]

Choi J, Fiszdon JM, Medalia A. Expectancy-Value Theory in Persistence of Learning Effects in Schizophrenia: Role of Task Value and Perceived Competency. Schizophrenia Bulletin. 2010; 36:957–965. [PubMed: 20634277]

Cicerone KD, Dahlberg C, Malec JF, Langenbahn DM, Felicetti T, Kneipp S, Ellmo W, Kalmar K, Giacino JT, Harley JP, Laatsch L, Morse PA, Catanese J. Evidence-based cognitive rehabilitation: updated review of the literature from 1998 through 2002. Archives of Physical Medicine & Rehabilitation. 2005; 86:1681–1692. [see comment]. [PubMed: 16084827]

Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, Felicetti T, Laatsch L, Harley JP, Bergquist T, Azulay J, Cantor J, Ashman T. Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 2003 Through 2008. Archives of Physical Medicine and Rehabilitation. 2011; 92:519–530. [PubMed: 21440699]

Cipriani G, Bianchetti A, Trabucchi M. Outcomes of a computer-based cognitive rehabilitation program on Alzheimer's disease patients compared with those on patients affected by mild cognitive impairment. Archives of Gerontology and Geriatrics. 2006; 43:327–335. [PubMed: 16451811]

Clare L, Jones RS. Errorless learning in the rehabilitation of memory impairment: A critical review. Neuropsychology Review. 2008; 18:1–23. [PubMed: 18247118]

Clare L, Linden DEJ, Woods RT, Whitaker R, Evans SJ, Parkinson CH, van Paasschen J, Nelis SM, Hoare Z, Yuen KSL, Rugg MD. Goal-Oriented Cognitive Rehabilitation for People With Early-Stage Alzheimer Disease: A Single-Blind Randomized Controlled Trial of Clinical Efficacy. American Journal of Geriatric Psych. 2010; 18:928–939.

Clare L, Wilson BA, Breen K, Hodges JR. Errorless learning of face-name associations in early Alzheimer's disease. Neurocase. 1999; 5:37–46.

Clare L, Wilson BA, Carter G, Hodges JR. Cognitive rehabilitation as a component of early intervention in Alzheimer's disease: A single case study. Aging & Mental Health. 2003a; 7:15–21. [PubMed: 12554310]

Clare L, Wilson BA, Carter G, Roth I, Hodges JR. Awareness in Early-Stage Alzheimer's Disease: Relationship to Outcome of Cognitive Rehabilitation. Journal of Clinical and Experimental Neuropsychology. 2004; 26:215–226. [PubMed: 15202541]

Clare L, Woods RT. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: A review. Neuropsychological Rehabilitation. 2004; 14:385–401.

Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2003b CD003260.

Cockburn J, Keene J. Neuropsychological rehabilitation. 2001

Cotelli M, Calabria M, Zanetti O. Cognitive rehabilitation in Alzheimer's Disease. Aging clinical and experimental research. 2006; 18:141–143. [PubMed: 16702783]

Cummings Jl CG. ALzheimer disease. JAMA: The Journal of the American Medical Association. 2002; 287:2335–2338. [PubMed: 11988038]

Dalla Barba G, Parlato V, Iavarone A, Boller F. Neuropsychology. 1995; 33:247.

Davis RN, Massman PJ, Doody RS. Cognitive Intervention in Alzheimer Disease: A Randomized Placebo-Controlled Study. Alzheimer Disease & Associated Disorders. 2001; 15:1–9. [PubMed: 11236819]

Derouesné C, Thibault S, Lagha-Pierucci S, Baudouin-Nadec V, Ancri D, Lacomblez L. International Journal of Geriatric Psychiatry. 1999; 14:1019. [PubMed: 10607969]

Ecklund-Johnson E, Torres I. Unawareness of Deficits in Alzheimer's Disease and Other Dementias: Operational Definitions and Empirical Findings. Neuropsychology Review. 2005; 15:147–166. [PubMed: 16328733]

Elgamal S, McKinnon MC, Ramakrishnan K, Joffe RT, MacQueen G. Successful computer-assisted cognitive remediation therapy in patients with unipolar depression: a proof of principle study. Psychological medicine. 2007; 37:1229–1238. [PubMed: 17610766]

Ernst, Rl; Hay, JW.; Fenn, C.; Tinklenberg, J.; Yesavage, JA. Cognitive function and the costs of alzheimer disease: An exploratory study. Archives of Neurology. 1997; 54:687–693. [PubMed: 9193203]

Farina E, Fioravanti R, Chiavari L, Imbornone E, Alberoni M, Pomati S, Pinardi G, Pignatti R, Mariani C. Comparing two programs of cognitive training in Alzheimer's disease: a pilot study. Acta Neurologica Scandinavica. 2002; 105:365–371. [PubMed: 11982487]

Feher EP, Mahurin RK, Inbody SB, Crook TH, et al. Anosognosia in Alzheimer's disease. Neuropsychiatry, Neuropsychology, & Behavioral Neurology. 1991; 4:136–146.

Fillit H, Hill J. The Economic Benefits of Acetylcholinesterase Inhibitors for Patients with Alzheimer Disease and Associated Dementias. Alzheimer Disease & Associated Disorders. 2004; 18:S24–S29. [PubMed: 15249845]

Fiszdon JM, Whelahan H, Bryson GJ, Wexler BE, Bell MD. Cognitive training of verbal memory using a dichotic listening paradigm: impact on symptoms and cognition. Acta Psychiatrica Scandinavica. 2005; 112:187–193. [PubMed: 16095473]

Folstein M, Folstein S, McHugh P. 'Mini Mental State': a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research. 1975; 12:189–198. [PubMed: 1202204]

Fry PS. Development of a geriatric scale of hopelessness: Implications for counseling and intervention with the depressed elderly. Journal of Counseling Psychology. 1984; 31:322–331.

Gao Y, Huang C, Zhao K, Ma L, Qiu X, Zhang L, Xiu Y, Chen L, Lu W, Huang C, Tang Y, Xiao Q. Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. International Journal of Geriatric Psychiatry. 2012 n/a-n/a.

Granholm E, Ben-Zeev D, Link PC. Social Disinterest Attitudes and Group Cognitive-Behavioral Social Skills Training for Functional Disability in Schizophrenia. Schizophrenia Bulletin. 2009; 35:874–883. [PubMed: 19628761]

Grant PM, Beck AT. Defeatist Beliefs as a Mediator of Cognitive Impairment, Negative Symptoms, and Functioning in Schizophrenia. Schizophrenia Bulletin. 2009; 35:798–806. [PubMed: 18308717]

Haier RJ, Siegel BV Jr, MacLachlan A, Soderling E, Lottenberg S, Buchsbaum MS. Regional glucose metabolic changes after learning a complex visuospatial/motor task: a positron emission tomographic study. Brain Research. 1992; 570:134–143. [PubMed: 1617405]

Hardy RM, Oyebode JR, Clare L. Measuring awareness in people with mild to moderate Alzheimer's disease: Development of the Memory Awareness Rating Scale–adjusted. Neuropsychological Rehabilitation. 2006; 16:178–193. [PubMed: 16565033]

Harwood DG, Sultzer DL. "Life Is Not Worth Living": Hopelessness in Alzheimer's Disease. Journal of Geriatric Psychiatry and Neurology. 2002; 15:38–43. [PubMed: 11936242]

Haupt M, Kurz A. Predictors of nursing home placement in patients with alzheimer's disease. International Journal of Geriatric Psychiatry. 1993; 8:741–746.

Heiss WD, Kessler J, Mielke R, Szelies B, et al. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease: A neuropsychological EEG, PET investigation. Dementia. 1994; 5:88–98. [PubMed: 8038871]

Horan WP, Rassovsky Y, Kern RS, Lee J, Wynn JK, Green MF. Further support for the role of dysfunctional attitudes in models of real-world functioning in schizophrenia. Journal of Psychiatric Research. 2010; 44:499–505. [PubMed: 20006849]

Huang C-Q, Wang Z-R, Li Y-H, Xie Y-Z, Liu Q-X. Cognitive function and risk for depression in old age: a meta-analysis of published literature. International Psychogeriatrics. 2011; 23:516–525. [PubMed: 20937170]

Huckans M, Pavawalla S, Demadura T, Kolessar M, Seelye A, Roost N, Twamley EW, Storzbach D. A pilot study examining effects of group-based Cognitive Strategy Training treatment on self-reported cognitive problems, psychiatric symptoms, functioning, and compensatory strategy use in OIF/OEF combat veterans with persistent mild cognitive disorder and history of traumatic brain injury. J Rehabil Res Dev. 2010; 47:43–60. [PubMed: 20437326]

Johannesen JK, Bodkins M, O'Donnell BF, Shekhar A, Hetrick WP. Perceptual anomalies in schizophrenia co-occur with selective impairments in the gamma frequency component of midlatency auditory ERPs. Journal of Abnormal Psychology. 2008; 117:106–118. [PubMed: 18266489]

Kern RS, Green MF, Mitchell S, Kopelowicz A, Mintz J, Liberman RP, Kern RS, Green MF, Mitchell S, Kopelowicz A, Mintz J, Liberman RP. Extensions of errorless learning for social problem-solving deficits in schizophrenia. American Journal of Psychiatry. 2005; 162:513–519. [PubMed: 15741468]

Kerns RD, Habib S. A Critical Review of the Pain Readiness to Change Model. The Journal of Pain. 2004; 5:357–367. [PubMed: 15501193]

Koltai DC, Welsh-Bohmer KA, Schmechel DE. Influence of anosognosia on treatment outcome among dementia patients. Neuropsychological Rehabilitation. 2001; 11:455–475.

Kurtz MM. Neurocognitive rehabilitation for schizophrenia. Current Psychiatry Reports. 2003; 5:303–310. [PubMed: 12857534]

Lincoln NB, Majid MJ, Weyman N. Cognitive rehabilitation for attention deficits following stroke. Cochrane Database Syst Rev. 2000 CD002842.

Loewenstein DA, Acevedo A, Czaja SJ, Duara R. Cognitive Rehabilitation of Mildly Impaired Alzheimer Disease Patients on Cholinesterase Inhibitors. American Journal of Geriatric Psych. 2004; 12:395–402.

Logsdon R, Gibbons L, McCurry S, Teri L. Assessing quality of life in older adults with cognitive impairment. Psychosomatic Medicine. 2002; 64:510–519. [PubMed: 12021425]

Logsdon RG, Gibbons LE, McCurry SM, Teri L. Quality of life in Alzheimer's disease: Patient and caregiver reports. Journal of Mental Health and Aging. 1999; 5:21–32.

Lopez OL, Becker JT, Sweet RA. Non-cognitive symptoms in mild cognitive impairment subjects. Neurocase. 2005; 11:65–71. [PubMed: 15804926]

Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biological Psychiatry. 2002; 52:243–252. [PubMed: 12182930]

Lysaker PH, Davis LW, Bryson GJ, Bell MD. Effects of cognitive behavioral therapy on work outcomes in vocational rehabilitation for participants with schizophrenia spectrum disorders. Schizophrenia Research. 2009; 107:186–191. [PubMed: 19046856]

Macquarrie CR. Experiences in early stage Alzheimer's disease: Understanding the paradox of acceptance and denial. Aging & Mental Health. 2005; 9:430–441. [PubMed: 16024402]

Mahncke HW, Bronstone A, Merzenich MM. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Progress in Brain Research. 2006a; 157:81–109. [PubMed: 17046669]

Mahncke HW, Connor BB, Appelman J, Ahsanuddin ON, Hardy JL, Wood RA, Joyce NM, Boniske T, Atkins SM, Merzenich MM. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. Proceedings of the National Academy of Sciences of the United States of America. 2006b; 103:12523–12528. [PubMed: 16888038]

Martire LM, Lustig AP, Schulz R, Miller GE, Helgeson VS. Is It Beneficial to Involve a Family Member? A Meta-Analysis of Psychosocial Interventions for Chronic Illness. Health Psychology. 2004; 23:599–611. [PubMed: 15546228]

McGlynn SM, Kaszniak AW. When Metacognition Fails: Impaired Awareness of Deficit in Alzheimer's Disease. Journal of Cognitive Neuroscience. 1991; 3:183–187.

Medalia A, Freilich B. The Neuropsychological Educational Approach to Cognitive Remediation (NEAR) Model: Practice Principles and Outcome Studies. American Journal of Psychiatric Rehabilitation. 2008; 11:123–143.

Michon A, Deweer B, Pillon B, Agid Y, Dubois B. Relation of anosognosia to frontal lobe dysfunction in Alzheimer's disease. Journal of Neurology, Neurosurgery & Psychiatry. 1994; 57:805–809.

Miller WR, Rollnick S. Ten Things that Motivational Interviewing Is Not. Behavioural and Cognitive Psychotherapy. 2009; 37:129–140. [PubMed: 19364414]

Miller WR, Rose GS. Toward a theory of motivational interviewing. American Psychologist. 2009; 64:527–537. [PubMed: 19739882]

Mittelman MS, Roth DL, Coon DW, Haley WE. Sustained benefit of supportive intervention for depressive symptoms in caregivers of patients with Alzheimer's disease. Am J Psychiatry. 2004; 161:850–856. [PubMed: 15121650]

Moore S, Sandman CA, McGrady K, Patrick Kesslak J. Memory training improves cognitive ability in patients with dementia. Neuropsychological Rehabilitation. 2001; 11:245–261.

National Institutes of Health, National Institute of Neurological Disorders and Stroke. [Accessed 7 November 2011] Alzheimer's disease information sheet. 2005. http://www.ninds.nih.gov/disorders/alzheimersdisease/alzeimersdisease.htm.

Olazarán J, Muñiz R, Reisberg B, Peña-Casanova J, del Ser T, Cruz-Jentoft AJ, Serrano P, Navarro E, García de la Rocha ML, Frank A, Galiano M, Fernández-Bullido Y, Serra JA, González-Salvador MT, Sevilla C. Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. Neurology. 2004; 63:2348–2353. [PubMed: 15623698]

Olesen PJ. Increased prefrontal and parietal activity after training of working memory. Nature neuroscience. 2004; 7:75.

Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, Santamato A, Vendemiale G, Seripa D, Pilotto A, Capurso A, Solfrizzi V. Late-Life Depression, Mild Cognitive Impairment, and Dementia: Possible Continuum? American Journal of Geriatric Psych. 2010; 18:98–116.

Potter GG, Steffens DC. Contribution of depression to cognitive impairment and dementia in older adults. The neurologist. 2007; 13:105–117. [PubMed: 17495754]

Reisberg B, Gordon B, McCarthy M, Ferris SH. Clinical symptoms accompanying progressive cognitive decline and Alzheimer's disease. Alzheimer's dementia. 1985:19–39.

Robert PH, Berr C, Volteau M, Bertogliati C, Benoit M, Sarazin M, Legrain S, Dubois B. Apathy in patients with mild cognitive impairment and the risk of developing dementia of Alzheimer's disease: A one-year follow-up study. Clinical Neurology and Neurosurgery. 2006; 108:733–736. [PubMed: 16567037]

Rohling ML, Faust ME, Beverly B, Demakis G. Effectiveness of cognitive rehabilitation following acquired brain injury: A meta-analytic re-examination of Cicerone etal.'s (2000, 2005) systematic reviews. Neuropsychology. 2009; 23:20–39. [PubMed: 19210030]

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. The American Journal of Psychiatry. 1984; 141:1356–1364. [PubMed: 6496779]

Sapolsky RM. Depression, antidepressants, and the shrinking hippocampus. Proceedings of the National Academy of Sciences. 2001; 98:12320–12322.

Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. Current Neurology and Neuroscience Reports. 2004; 4:374–380. [PubMed: 15324603]

Schulz R, Martire LM. Family Caregiving of Persons With Dementia: Prevalence, Health Effects, and Support Strategies. American Journal of Geriatric Psych. 2004; 12:240–249.

Seelaar H, Rohrer JD, Pijnenburg YAL, Fox NC, van Swieten JC. Clinical, genetic and pathological heterogeneity of frontotemporal dementia: a review. Journal of Neurology, Neurosurgery & Psychiatry. 2011; 82:476–486.

Sitzer DI, Twamley EW, Jeste DV. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. Acta Psychiatrica Scandinavica. 2006; 114:75–90. [PubMed: 16836595]

Small GW, Silverman DHS, Siddarth P, Ercoli LM, Miller KJ, Lavretsky H, Wright BC, Bookheimer SY, Barrio JR, Phelps ME. Effects of a 14-Day Healthy Longevity Lifestyle Program on Cognition and Brain Function. American Journal of Geriatric Psych. 2006; 14:538–545.

Smith CA, Henderson VW, McCleary CA, Murdock GA, Buckwalter JG. Anosognosia and Alzheimer's Disease: The Role of Depressive Symptoms in Mediating Impaired Insight. Journal of Clinical and Experimental Neuropsychology. 2000; 22:437–444. [PubMed: 10923053]

Spector A, Davies S, Woods B, Orrell M. Reality Orientation for Dementia: A Systematic Review of the Evidence of Effectiveness from Randomized Controlled Trials. The Gerontologist. 2000; 40:206–212. [PubMed: 10820923]

Spector A, Orrell M, Woods B. Cognitive Stimulation Therapy (CST): effects on different areas of cognitive function for people with dementia. International Journal of Geriatric Psychiatry. 2010; 25:1253–1258. [PubMed: 20069533]

Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, Orrell M. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry. 2003; 183:248–254. [PubMed: 12948999]

Spector A, Woods B, Orrell M. Cognitive stimulation for the treatment of Alzheimer's disease. Expert Review of Neurotherapeutics. 2008; 8:751–757. [PubMed: 18457532]

Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. Am J Psychiatry. 2005; 162:2086–2093. [PubMed: 16263848]

Steenland K, Karnes C, Seals R, Carnevale C, Hermida A, Levey A. Late-Life Depression as a Risk Factor for Mild Cognitive Impairment or Alzheimer's Disease in 30 US Alzheimer's Disease Centers. Journal of Alzheimer's Disease. 2012; 31:265–275.

Stern Y. Cognitive Reserve and Alzheimer Disease. Alzheimer Disease & Associated Disorders. 2006; 20:112–117. [PubMed: 16772747]

Suarez M. Motivational Interviewing: Preparing People for Change, 2nd Edition. Journal of Developmental & Behavioral Pediatrics. 2006; 27:417.

Sunderland A, Harris JE, Baddeley AD. Do laboratory tests predict everyday memory? A neuropsychological study. Journal of Verbal Learning and Verbal Behavior. 1983; 22:341–357.

Talassi E, Guerreschi M, Feriani M, Fedi V, Bianchetti A, Trabucchi M. Effectiveness of a cognitive rehabilitation program in mild dementia (MD) and mild cognitive impairment (MCI): A case control study. Archives of Gerontology and Geriatrics. 2007; 44(Supplement):391–399. [PubMed: 17317481]

Tárraga L, Boada M, Modinos G, Espinosa A, Diego S, Morera A, Guitart M, Balcells J, López OL, Becker JT. A randomised pilot study to assess the efficacy of an interactive, multimedia tool of cognitive stimulation in Alzheimer's disease. Journal of Neurology, Neurosurgery & Psychiatry. 2006; 77:1116–1121.

Twamley EW, Savla GN, Zurhellen CH, Heaton RK, Jeste DV. Development and pilot testing of a novel compensatory cognitive training intervention for people with psychosis. American Journal of Psychiatric Rehabilitation. 2008; 11:144–163. [PubMed: 19198664]

Twamley EW, Vella L, Burton CZ, Heaton RK, Jeste DV. Compensatory cognitive training for psychosis: effects in a randomized controlled trial. J Clin Psychiatry. 2012; 73:1212–1219. [PubMed: 22939029]

Valenzuela M, Sachdev P. Can Cognitive Exercise Prevent the Onset of Dementia? Systematic Review of Randomized Clinical Trials with Longitudinal Follow-up. American Journal of Geriatric Psych. 2009; 17:179–187.

van Dyck CH. Understanding the latest advances in pharmacologic interventions for Alzheimer's disease. CNS spectrums. 2004; 9:24–28. [PubMed: 15241297]

van Dyck CH, Tariot PN, Meyers B, Malca Resnick E. Group, f.t. M. M. -M.-S. A 24-week Randomized, Controlled Trial of Memantine in Patients With Moderate-to-severe Alzheimer Disease. Alzheimer Disease & Associated Disorders. 2007; 21:136–143. [PubMed: 17545739]

Vocci FJ. Cognitive remediation in the treatment of stimulant abuse disorders: A research agenda. Experimental and Clinical Psychopharmacology. 2008; 16:484–497. [PubMed: 19086769]

Weinstein EA. Anosognosia and denial of illness. Awareness of deficit after brain injury: Clinical and theoretical issues. 1991:240–257.

Wexler BE, Bell MD. Cognitive remediation and vocational rehabilitation for schizophrenia. Schizophrenia Bulletin. 2005; 31:931–941. [PubMed: 16079390]

Wigfield A, Eccles JS. Expectancy–Value Theory of Achievement Motivation. Contemporary Educational Psychology. 2000; 25:68–81. [PubMed: 10620382]

Wilson BA. Towards a comprehensive model of cognitive rehabilitation. Neuropsychological Rehabilitation. 2002; 12:97–110.

Woods RT. Discovering the person with Alzheimer's disease: Cognitive, emotional and behavioural aspects. Aging & Mental Health. 2001; 5:7–16.

Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry. 2011; 168:472–485. [PubMed: 21406461]

Wykes T, Spaulding WD. Thinking About the Future Cognitive Remediation Therapy—What Works and Could We Do Better? Schizophrenia Bulletin. 2011; 37:S80–S90. [PubMed: 21860051]
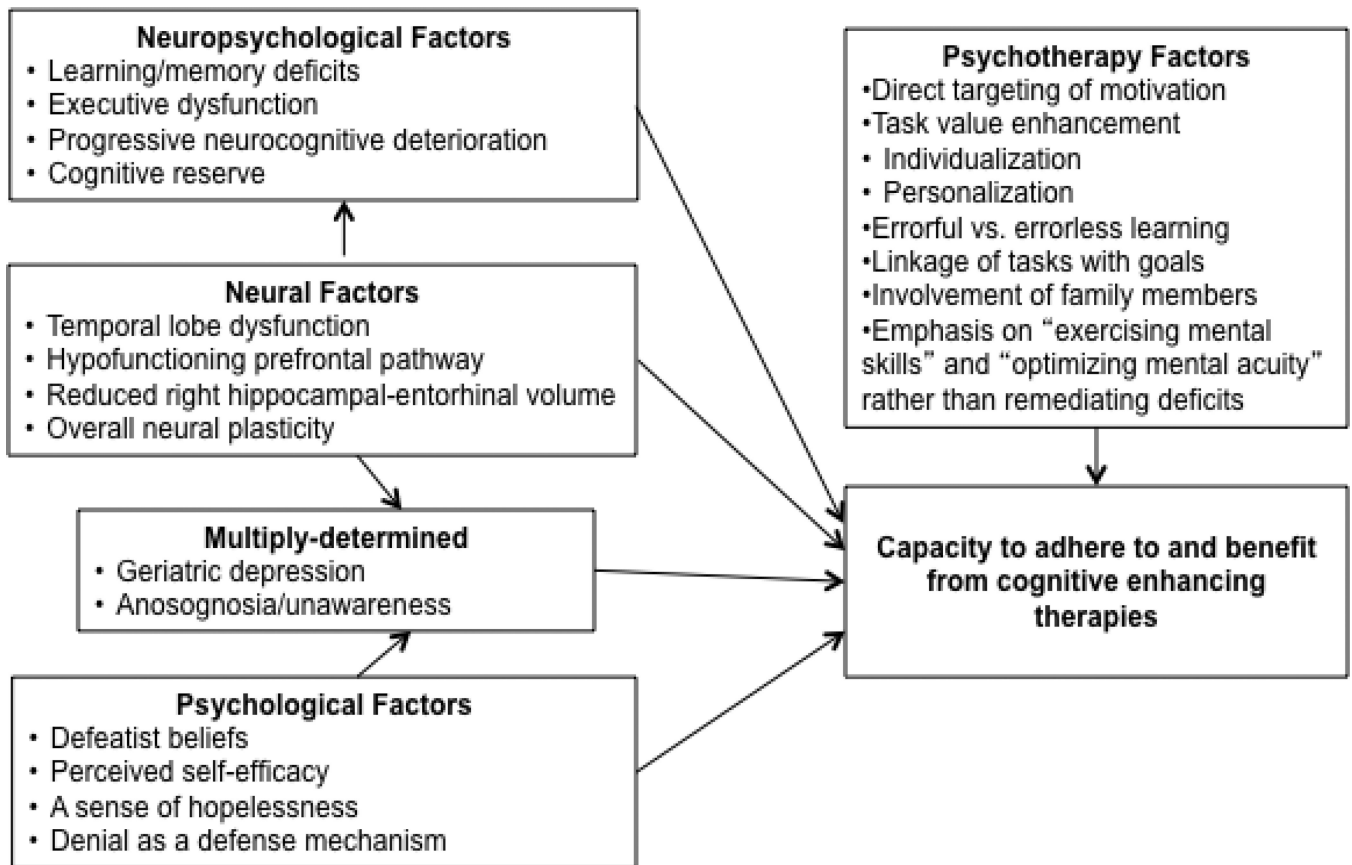
Fig. 1.
Putative determinants of cognitive enhancing therapy outcome in Alzheimer's disease