

Cognitive Training for Early-Stage Alzheimer's Disease and Dementia

By: Fang Yu, Karen M. Rose, Sandra C. Burgener, Cindy Cunningham, Linda L. Buettner, Elizabeth Beattie, Ann L. Bossen, Kathleen C. Buckwalter, Donna M. Fick, Suzanne Fitzsimmons, Ann Kolanowski, Janet K. Pringle Specht, Nancy E. Richeson, Ingelin Testad, and Sharon E. McKenzie

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Abstract:

The purpose of this article is to critically review and synthesize the literature on the effects of nonpharmacological cognitive training on dementia symptoms in early-stage Alzheimer's disease (AD) and related dementia. Electronic databases MEDLINE (PubMed), CINAHL, PsycInfo, and the Cochrane Library were searched using the keywords cognition, reality orientation, Alzheimer's disease, psychosocial factors, cognitive therapy, brain plasticity, enriched environments, and memory training. The findings support that cognitive training improves cognition, activities of daily living, and decision making. Interventions are more effective if they are structured and focus on specific known losses related to the AD pathological process and a person's residual ability, or are combined with cognitive-enhancing medications. Nursing implications are also discussed.

Article:

Individuals differ considerably in their cognitive capability and their susceptibility to aging and neurodegenerative diseases. The concept of cognitive reserve is used to explain these differences, supporting that there is no simple threshold model for the pathology that leads to impaired cognitive function (Whalley, Deary, Appleton, & Starr, 2004). Cognitive impairment is likely a product of multiple factors, including individual differences in intelligence, methods for processing tasks, occupation, education, work environment, coping skills for stressful experiences, choice of cognitively stimulating leisure pursuits, and use of health services (Stern, 2006; Whalley et al., 2004).

Recent scientific advances suggest that after damage the human brain can reorganize and experience functional improvements, even in cases of neurodegenerative diseases such as Alzheimer's disease (AD) (Bach-y-Rita, 2003). Neurons affected by AD exhibit atrophic changes and metabolic impairments, which may contribute to neuronal dysfunction (Swaab, Dubelaar, Scherder, van Someren, & Verwer, 2003). Neuronal damage used to be considered irrecoverable, but neurons are now understood to be plastic and regenerative (Bach-y-Rita, 2003). It is postulated that neurons might work through nonsynaptic neurotransmission in which communication between cells takes place not through connected synapses, but rather through the release of neurotransmitters from remote sites that can be trained to assume the function previously performed by the injured brain (Bach-y-Rita, 2003).

In animal models, neuronal stimulation and rehabilitation can be achieved through environmental enrichment. For example, compared with animals in standard cages, animals housed in environments with access to novel objects, exercise wheels, and a large number of cage mates had significantly improved brain structure and function (Jankowsky et al., 2005). Using functional magnetic resonance imaging, individuals with early-stage AD demonstrated increased activation of several cortical areas when engaged in cognitive tasks, indicating

functional compensation for neuronal loss (Rocca & Filippi, 2006). Findings such as these suggest that improving or maintaining cognitive function through cognitive stimulation/rehabilitation is biologically plausible. The enhancement of cognitive reserves has the potential to delay progression of cognitive impairment and improve quality of life in individuals with AD.

The purpose of this article is to critically review, synthesize, and grade the literature on the effects of cognitive training in individuals with early-stage AD. Electronic databases MEDLINE (PubMed), CINAHL, PsycInfo, and the Cochrane Library were searched using the keywords cognition, reality orientation, Alzheimer's disease, psychosocial factors, cognitive therapy, brain plasticity, enriched environments, and memory training.

Findings

Cognitive training refers to any nonpharmacological intervention designed to improve cognition, regardless of mechanism of action. Typically, cognitive training focuses on specific cognitive domains or cognitively mediated domains of functioning, such as basic and instrumental activities of daily living (ADLs), social skills, and behavioral disturbances (Sitzer, Twamley, & Jeste, 2006). Cognitive training includes cognitive stimulation, memory rehabilitation, reality orientation, and neuropsychological rehabilitation.

Cognitive stimulation refers to nonregimental involvement in activities that require mental functioning and is less formally programmed than other kinds of cognitive training. Stimulation activities can be either active or passive. Examples of active activities are group discussion of current events or solving a crossword puzzle. Passive activities include observing nature, listening to a poetry reading or music, or watching a play.

Memory rehabilitation is based on the hypothesis that memory loss in AD results from defective encoding and storage of information rather than forgetting information (Metzler-Baddely & Snowden, 2005). It focuses on encoding information in areas of the brain that are less affected by AD. Memory training has three characteristics:

- Specifically targets encoding of memory and recall.
- Typically examines the effect of one training method per study.
- Targets the location of active pathology and function of that area.

Reality orientation relates information such as person, place, and time to individuals with AD and can be done continually or as a classroom technique (Spector, Davies, Woods, & Orrel, 2000). During continual orientation, the person with AD is involved in reality-based communication with every contact throughout their day. In classroom reality orientation, groups meet on a regular basis to engage in orientation-related activities.

Neuropsychological rehabilitation in AD aims to optimize functions, minimize excessive disability risk, and prevent the development of negative social psychology. It is a process of actively changing and enabling people to achieve an optimal level of physical, psychological, and social function and is used across areas of physical health, psychological well-being, ADLs, and social relationships (Avila et al., 2004).

The Effect of Cognitive Stimulation

Research suggests that cognitive stimulation is effective at improving cognition and that a combination of cognitive stimulation and medication is the most effective. In a 1-year randomized controlled trial (RCT), 86 participants with mild AD at an adult day center in Spain were assigned to one of four groups: combined donepezil (Aricept®) and cognitive stimulation, donepezil alone, cognitive stimulation alone, and a control group. At 1-year follow up, participants in the combined group had improvements in their average Mini-Mental State Examination (MMSE) score (from 22.95 to 24.45). Cognitive stimulation alone also increased the MMSE score, but to a lesser extent. The medication only and control groups showed declines in MMSE scores (from 21.17 to 17.80, and 19.39 to 13.11, respectively) (Requena et al., 2004, evidence grade: A2). At 2-year follow up, all four groups showed declines in MMSE scores, with the fastest decline observed in the control group. The

group receiving a combination of medication and cognitive stimulation had the least decline, and those participants' MMSE scores were significantly higher than those of the control group (Requena, Maestú, Campo, Fernández, & Ortiz, 2006, evidence grade: A2).

In a similarly designed U.S. study, investigators compared the effects of cognitive stimulation in combination with donepezil and donepezil alone in a group of 54 adults with mild to moderate AD (median MMSE score at baseline = 20.87). Training consisted of education on AD, communication techniques, and instruction on how to create a life story book. The group met for 1 to 1.5 hours once per week for 8 weeks. Compared with the medication-only group, participants in the combination group showed slower decline in MMSE scores, less irritability, less apathy, and improved quality of life after completion of the training (Chapman, Weiner, Rackley, Hynan, & Zientz, 2004, evidence grade: B2).

The Effect of Cognitive Training

In a study by Hoffman, Hock, and Müller-Spahn (1996), a computer-based training program was used to instruct 4 adults with mild to moderate AD in functional tasks. Photographs of the steps in tasks to be learned were taken and scanned into a computer. Participants then used the touch screen of the computer to sequence the tasks. A facilitator was present to offer advice, but participants were encouraged to work as independently as possible. All 4 participants' training performance improved substantially, but overall cognitive improvement was not observed (Hoffman et al., 1996, evidence grade: C1).

In an RCT of 37 individuals with early-stage AD, 19 participated in 5 weeks of cognitive training that included all of the following: spaced retrieval, in which participants were taught information and then repeatedly tested on it; a cognitive stimulation program; and a training program on face-name associations (Davis, Massman, & Doody, 2001). After 5 weeks, participants continued the intervention at home for 30 minutes daily, 6 days per week. The remaining participants were assigned to a 5-week placebo program that consisted of watching general health videos, participating in interviews with the investigators, and engaging in unstructured conversations. After the initial 5-week treatment, participants were reassessed, and the placebo group then received the intervention. The intervention group improved in the specific areas in which they received training; however, these gains did not translate to improved quality of life or overall neuropsychological functioning (Davis et al., 2001, evidence grade: A2).

Similar to findings from cognitive stimulation, a combination of cognitive training and medication showed better improvement in cognition in individuals with AD. Their MMSE scores increased from an average of 23.50 to 24.33 at the end of the 5-month study, while the medication-only group declined from 21.29 to 19.86 (Bottino et al., 2005, evidence grade: A2).

A recent meta-analysis of studies testing cognitive training for early-stage AD between 1980 and 2004 supports that cognitive training is effective. Specifically, medium effect sizes were observed for learning, memory, executive functioning, ADLs, general cognitive problems, depression, and self-rated general functioning (Sitzer et al., 2006, evidence grade: A1).

The Effect of Memory Rehabilitation

Techniques used in memory training include explicit learning, errorless learning, errorful learning, implicit learning, and memory aids. Explicit learning is purposeful and occurs when people use rote memorization and verbally oriented learning in a conscious process to create a memory or learn a skill. Explicit memory is first kind of memory to be impaired in AD. Implicit memory is nonverbal and observational and may be accomplished during the course of an activity unrelated to what is being learned, such as practice of motor skills. It is considered to be automatic and is not performed on a conscious basis. Implicit memory remains intact until the more severe stages of dementia and is enhanced through the use of environmental cues in learning (Sitzer et al., 2006). Errorless learning is a learning approach that avoids, or at least limits, errors during the acquisition phase of learning, thereby reducing the chances of reinforcement of incorrect information. Errorful learning focuses on correcting mistakes made during the acquisition phase of learning. Memory aids include different

devices such as an electronic memory aid (EMA), a device that uses an alarm system to alert the user to a message regarding an appointment or task to facilitate memory and learning (Lowenstein, 2004; Metzler-Baddely & Snowden, 2005; Sitzer et al., 2006).

Explicit Learning Strategies. Two studies were found that tested explicit learning strategies. One study used a mnemonics technique to improve face-name recall with 8 participants, 6 with early-stage AD. Only 1 participant showed an improvement in recall (Bäckman, Josephsson, Herlitz, Stigsdotter, & Viitanen, 1991, evidence grade: C2). In an RCT by Cahn-Weiner, Malloy, Rebok, and Ott (2003), half of a sample of 34 individuals with early-stage AD were assigned to 6 weeks of memory training (practice of mnemonics, organization of items to be recalled into categories, and visualizing and associating memories) and the other half to the control condition. All of the participants were receiving cholinesterase inhibitors. Although no statistically significant difference was found in memory and ADLs scores between the two groups, more learning did occur in the memory training group (Cahn-Weiner et al., 2003, evidence grade: A2).

Errorless Learning Strategies. In a study of 6 participants with early-stage AD, errorless learning techniques were found to be beneficial in improving everyday memory tasks (Clare, Wilson, Carter, & Hodges, 2003, evidence grade: C1). In another study, errorless learning techniques were also used with 12 participants with early-stage AD to relearn face-name associations (Clare, Wilson, Carter, Roth, & Hodges, 2002, evidence grade: C1). The intervention resulted in improved recall of the trained items that was maintained without training for 6 months. Kixmiller (2002) trained 5 individuals with early-stage AD using an errorless learning method in a prospective memory task. Two participants with mild AD served as controls and received instruction in the prospective memory task without the use of errorless learning. The intervention group performed significantly better in the prospective memory task than the control group (Kixmiller, 2002, evidence grade: A2). However, not all participants benefited from errorless learning. Those who were aware of their diagnosis and deficits and had higher MMSE scores benefited the most (Clare et al., 2002).

Other studies have compared the effect of errorful versus errorless memory training. One study evaluated 4 individuals with AD, 3 with MMSE scores of 21 or greater, and 1 with an MMSE score of 11 (MetzlerBaddely & Snowden, 2005). The 4 participants were taught both novel and familiar materials using errorful and errorless learning techniques. All 4 learned some of the material presented, with errorless learning techniques resulting in modestly better memory outcomes than errorful techniques (Metzler-Baddely & Snowden, evidence grade: C2). In another study, 3 individuals with AD were compared with 8 control participants, matched on age and educational levels. Errorless learning improved recall of low-level knowledge in both groups (Haslam, Gilroy, Black, & Beesley, 2006, evidence grade: C2).

Implicit Learning Strategies. In an RCT by Zanetti et al. (1997, evidence grade: A2), 10 adults with mild to moderate AD participated in an implicit learning intervention that emphasized the motor skills for performing ADLs: 5 participants learned 10 of 20 activities, and 5 learned the remaining 10 activities over 3 weeks. Ten healthy elderly participants served as the control group. After 3 weeks, the intervention groups improved significantly in the trained activities and nontrained activities, while the control participants evidenced no improvement.

Memory Aids. The efficacy of memory aids has been investigated in small samples of individuals with early-stage AD. In one study, 15 participants with AD were assigned to three groups (5 people per group): an EMA group, a control group that enhanced recall using a written list, and a second control group that enhanced recall without any external memory aid (Oriani et al., 2003). Results showed that the EMA group yielded significantly better results on recall than both control conditions (evidence grade: C1). The advantage of memory aids was also reported in a case study of a person with early-stage AD who showed improvement in ADLs after using a digital clock and a memory book for 3 months, despite a decline in the participant's MMSE score (Quitte, Olivier, & Salmon, 2005, evidence grade: C1).

In an RCT by Schreiber, Schweizer, Lutz, Kalveram, and Jäncke (1999), participants with mild to moderate AD or vascular dementia were randomized into treatment (n = 7) and control (n = 7) groups to test the efficacy of an interactive computer program (MULTITASK). The MULTITASK program included training for immediate and delayed recall of objects and routes, with each session lasting 10 to 30 minutes, while the control group was engaged in conversations with a psychologist. Following training, treatment participants showed improvements in im-

KEYPOINTS

COGNITIVE TRAINING

Yu, F., Rose, K.M., Burgener, S.C., Cunningham, C., Buettner, L.L., Beattie, E., et al. (2009). *Cognitive Training for Early-Stage Alzheimer's Disease and Dementia*. *Journal of Gerontological Nursing*, 35(3), 23-29.

- 1 The human brain can reorganize after damage and experience functional improvements, even in neurodegenerative diseases such as Alzheimer's disease (AD).
- 2 Cognitive training is likely to be effective for managing symptoms in individuals with early-stage AD and dementia.
- 3 Evidence for the effectiveness of other cognitive enhancement programs such as memory aids, neuropsychological rehabilitation, and reality orientation for managing certain symptoms is emerging, but studies are few and results are mixed.

mediate recall of objects and in immediate and delayed recall of routes in their environment as compared with control participants (Schreiber et al., 1999, evidence grade: A2).

The Effect of Reality Orientation

Reality orientation has mainly been used in Europe. In an RCT by Zanetti et al. (1995), 16 participants received cycles of 1-month reality orientation classes with breaks of 5 to 7 weeks between cycles. At the conclusion of the 8-month study, participants in the reality orientation group demonstrated mild improvements in their median MMSE score (0.69 points), while median MMSE scores in the control group declined 2.58 points (Zanetti et al., 1995, evidence grade: A2). Two meta-analyses (Cotelli, Calabria, & Zanetti, 2006; Spector et al., 2000) supported a positive effect of classroom reality orientation on cognition (evidence grades: A1 and D, respectively), while the study with the largest sample found a 2.1 point increase in MMSE scores for the treatment group compared with the control group.

The combined effect of reality orientation and donepezil versus donepezil alone was further explored in 156 participants (Onder et al., 2005, evidence grade: A2). Caregivers of the reality orientation group were required to participate in the program at home for 30 minutes per day, three times per week over 25 consecutive weeks. The treatment group experienced a 0.2-point gain in MMSE scores, while the control group had a decline of 1.1 points.

The Effect of Neuropsychological Rehabilitation

Limited research is available regarding the effect of neuropsychological rehabilitation in individuals with early-stage AD. In a case study by Fernández, Manoilloff, and Monti (2006), one man with AD was followed over 34 months and was treated with two different cholinesterase inhibitors at different times, which alternated with neuropsychological rehabilitation. Although the participant did experience cognitive decline over time, the decline occurred at a much slower rate than would be projected (Fernández et al., 2006, evidence grade: D1). In another study, 5 participants with mild AD received a 14-week neuropsychological rehabilitation intervention (memory training, repeated motor movements, verbal associations and categorization, and ADLs training) and

showed significant improvements in cognition and ADLs at the end of the rehabilitation (Avila et al., 2004, evidence grade: C1).

COMPARING EFFECTS OF DIFFERENT COGNITIVE TRAINING

To facilitate individualized care, it is essential to conduct efficacy studies of different cognitive training interventions. Research findings, however, are limited, with most studies concentrated on comparing cognitive training and cognitive stimulation. In one study, 32 individuals with early-stage AD were assigned to a cognitive stimulation group (e.g., conversation, singing, dancing, party games, and creative pursuits) or specific cognitive training group (e.g., procedural memory training on ADLs and neuropsychological rehabilitation of residual functions) for 6 weeks. Both groups showed improvement in ADLs performance, but the cognitive stimulation group evidenced greater improvement in behavioral disturbances and ADLs (Farina et al., 2006, evidence grade: B2). In another study, 22 adults with mild to moderate AD were assigned to receive procedural memory training on 24 different ADLs or to receive training of residual cognitive functions such as attention, memory, and language. At the end of the training, both groups displayed improvement in ADLs, with the group receiving the procedural memory training showing higher levels of improvement (Farina et al., 2002, evidence grade: C1).

Although the above findings are encouraging, it is also puzzling why certain interventions might yield better outcomes than others. One potential confounding factor is the use of cholinergic medications in some studies. Controlling for medication use, the effect of cognitive training was compared with cognitive stimulation in a 3-month RCT of 44 individuals with mild AD (Lowenstein, 2004, evidence grade: C1). In this study, all participants were stabilized on a cholinesterase inhibitor and randomly assigned to a cognitive training or stimulation group and participated in sessions lasting 24 to 45 minutes over 12 to 16 weeks. Cognitive stimulation included spaced retrieval, dual cognitive support, and procedural memory training. Cognitive stimulation incorporated commercially available computer games that required the participant to match pairs of letters, numbers, or designs from memory; exercises such as Hangman; tasks that required the participant to find words distributed in an array of letters; topic-of-the-day discussions (reminiscence); and review and discussion of homework. At the end of the study and 3-month follow up, the cognitive training group demonstrated improvement, while cognitive gains were not consistent in the cognitive stimulation group (Lowenstein, 2004).

NURSING IMPLICATIONS

Emerging scientific evidence supports that various cognitive training interventions improve cognition, memory, learning, problem solving, and ADLs performance. Well-characterized interventions appear to have better outcomes compared with less-defined interventions, which in turn, are better than no interventions. The average MMSE improvement was approximately 1.5, while the comparison groups declined. These findings suggest that cognitive training may be an important intervention for people with AD because they typically decline 3 points on the MMSE per year.

These findings have important nursing implications. First, AD is often perceived as a progressive, disabling disease with limited opportunities for clinicians to work toward improvement. This review suggests that despite the progressive nature of dementia, individuals with AD can still learn and maintain their cognitive capacity through cognitive training. The old adage of “use it or lose it” holds true.

Second, most of the cognitive interventions are easy to learn and incorporate into nursing practice either in individual or group sessions. Further, the interventions do not cause adverse events, which are often associated with medication use. Nurses could also collaborate with other disciplines, such as psychology, occupational therapy, and recreational therapy, to develop training programs and train nursing assistants or activity coordinators to integrate cognitive training exercises into their daily practice.

Third, due to their educational background and clinical skills, nurses often possess unique knowledge about their older clients, which makes the development and implementation of individualized care a reality. The

different cognitive training interventions discussed in this article offer a variety of techniques that nurses could select, identifying those that are most suitable to their practice setting and clientele.

Fourth, the available research findings suggest that cognitive training works best when combined with medication. Thus, nurses could advocate for both a cognitive training and pharmacological treatment for their clients. Although nurses are not currently paid to do cognitive training with today's reimbursement mechanisms, policy changes could be facilitated with mounting research evidence.

On a cautionary note, many studies reviewed in this article had small samples. The study findings about individuals with early-stage AD might not hold if larger samples were used, or may not be applicable to later stages, as well as other dementias, such as frontal temporal dementia (FTD) and Lewy body dementia (LBD), as those dementias manifest different disease mechanisms, symptoms, and progressions (Boeve, 2005; Stewart, 2006). Individuals with FTD or LBD might have difficulty attending to tasks or training and may not be good candidates for the kinds of nonpharmacological interventions included in this review.

CONCLUSION

Cognitive training shows great potential as a nonpharmacological approach to augment the treatment of early-stage AD, although its efficacy and long-term effects have yet to be established. Interventions structured to target known losses related to AD pathological processes and a person's residual ability might have greater cognitive benefits. Thus, geriatric nurses are in an ideal position to promote the use of cognitive training in dementia.

REFERENCES

- Avila, R., Bottino, C.M.C., Carvalho, I.A.M., Santos, C.B., Seral, C., & Miotto, E.C. (2004). 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*, *37*, 1721-1729.
- Bach-y-Rita, P. (2003). Theoretical basis for brain plasticity after TBI. *Brain Injury*, *17*, 643-651.
- Bäckman, L., Josephsson, S., Herlitz, A., Stigsdotter, A., & Viitanen, M. (1991). The generalizability of training gains in dementia: Effects of an imagery-based mnemonic on face-name retention duration. *Psychology and Aging*, *6*, 489-492.
- Boeve, B.F. (2005). Clinical, diagnostic, genetic and management issues in dementia with lewy bodies. *Clinical Science*, *109*, 343-354.
- Bottino, C.M., Carvalho, I.A., Alvarez, A.M., Avila, R., Zukauskas, P.R., Bustamante, S.E., et al. (2005). Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: A pilot study. *Clinical Rehabilitation*, *19*, 861-869.
- Cahn-Weiner, D.A., Malloy, P.F., Rebok, G.W., & Ott, B.R. (2003). Results of randomized placebo-controlled study of memory training for mildly impaired Alzheimer's disease patients. *Applied Neuropsychology*, *10*, 215-223.
- Chapman, S.B., Weiner, M.F., Rackley, A., Hynan, L.S., & Zientz, J. (2004). Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *Journal of Speech, Language, and Hearing Research*, *47*, 1149-1163.
- Clare, L., Wilson, B.A., Carter, G., & Hodges, J.R. (2003). Cognitive rehabilitation as a component of early intervention in Alzheimer's disease: A single case. *Aging & Mental Health*, *7*, 15-21.
- Clare, L., Wilson, B.A., Carter, G., Roth, I., & Hodges, J.R. (2002). Relearning face-name associations in early Alzheimer's disease. *Neuropsychology*, *16*, 538-547.
- Cotelli, M., Calabria, M., & Zanetti, O. (2006). Cognitive rehabilitation in Alzheimer's disease. *Aging Clinical and Experimental Research*, *18*, 141-143.
- Davis, R.N., Massman, P.J., & Doody, R.S. (2001). Cognitive intervention in Alzheimer's disease: A randomized placebo-controlled study. *Alzheimer Disease and Associated Disorders*, *15*, 1-9.
- Farina, E., Fioravanti, R., Chiavari, L., Imbornone, E., Alberoni, M., Pomati, S., et al. (2002). Comparing two programs of cognitive training in Alzheimer's disease: A pilot study. *Acta Neurologica Scandinavica*, *105*, 365-371.

- Farina, E., Mantovani, F., Fioravanti, R., Pignatti, R., Chiavari, L., Imbornone, E., et al. (2006). Evaluating two group programmes of cognitive training in mild-to-moderate AD: Is there any difference between a "global" stimulation and a "cognitive-specific" one? *Aging & Mental Health*, *10*, 211-218.
- Fernández, A.L., Manoiloff, L.M., & Monti, A.A. (2006). Long-term cognitive treatment of Alzheimer's disease: A single case study. *Neuropsychological Rehabilitation*, *16*, 96-109.
- Haslam, C., Gilroy, D., Black, S., & Beesley, T. (2006). How successful is errorless learning in supporting memory for high and low level knowledge in dementia? *Neuropsychological Rehabilitation*, *16*, 505-536.
- Hoffman, M., Hock, C., & Müller-Spahn, F. (1996). Computer-based cognitive training in Alzheimer's disease patients. *Annals of the New York Academy of Sciences*, *777*, 249-254.
- Jankowsky, J.L., Melnikova, T., Fadale, D.J., Xu, G.M., Slunt, H.H., Gonzales, V., et al. (2005). Environmental enrichment mitigates cognitive deficits in a mouse model of Alzheimer's disease. *Journal of Neuroscience*, *25*, 5217-5224.
- Kixmiller, J.S. (2002). Evaluation of prospective memory training for individuals with mild Alzheimer's disease. *Brain and Cognition*, *49*, 237-241.
- Lowenstein, D. (2004). Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. *American Journal of Geriatric Psychiatry*, *12*, 395-402.
- Metzler-Baddely, C., & Snowden, J.S. (2005). Brief report: Errorless versus errorful learning as a memory rehabilitation approach in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology*, *27*, 1070- 1079.
- Onder, G., Zanetti, O., Giacobini, E., Frisoni, G.B., Bartorelli, L., Carbone, G., et al. (2005). Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: Randomized controlled trial. *British Journal of Psychiatry*, *187*, 450-455.
- Oriani, M., Moniz-Cook, E., Binetti, G., Zanieri, G., Frisoni, G.B., Geroldi, C., et al. (2003). An electronic memory aid to support prospective memory in patients in the early stages of Alzheimer's disease: A pilot study. *Aging & Mental Health*, *7*, 22-27.
- Quittre, A., Olivier, C., & Salmon, E. (2005). Compensating strategies for impaired episodic memory and time orientation in a patient with Alzheimer's disease. *Acta Neurologica Belgica*, *105*, 30-38.
- Requena, C., López Ibor, M.I., Maestú, F., Campo, P., López Ibor, J.J., & Ortiz, T. (2004). Effects of cholinergic drugs and cognitive training on dementia. *Dementia and Geriatric Cognitive Disorders*, *18*, 50-54.
- Requena, C., Maestú, F., Campo, P., Fernández, A., & Ortiz, T. (2006). Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. *Dementia and Geriatric Cognitive Disorders*, *22*, 339-345.
- Rocca, M.A., & Filippi, M. (2006). Functional MRI to study brain plasticity in clinical neurology. *Neurological Sciences*, *27*(Suppl. 1), S24-S26.
- Schreiber, M., Schweizer, A., Lutz, K., Kalveram, K.T., & Jäncke, L. (1999). Potential of an interactive computer-based training in the rehabilitation of dementia: An initial study. *Neuropsychological Rehabilitation*, *9*, 155-167.
- Sitzer, D.I., Twamley, E.W., & Jeste, D.V. (2006). Cognitive training in Alzheimer's disease: A meta-analysis of the literature. *Acta Psychiatrica Scandinavica*, *114*, 75- 90.
- Spector, A., Davies, S., Woods, S., & Orrel, M. (2000). Reality orientation for dementia: A systematic review of the evidence of effectiveness from randomized controlled trials. *The Gerontologist*, *40*, 206-212.
- Stern, Y. (2006). Cognitive reserve and Alzheimer disease. *Alzheimer Disease and Associated Disorders*, *20*, 112-117.
- Stewart, J.T. (2006). The frontal/subcortical dementias: Common dementing illnesses associated with prominent and disturbing behavioral changes. *Geriatrics*, *61*(8), 23-27.
- Swaab, D.F., Dubelaar, E.J., Scherder, E.J., van Someren, E.J., & Verwer, R.W. (2003). Therapeutic strategies for Alzheimer disease: Focus on neuronal reactivation of metabolically impaired neurons. *Alzheimer Disease and Associated Disorders*, *17*(Suppl. 4), S114-S122.
- Whalley, L.J., Deary, I.J., Appleton, C.L., & Starr, J.M. (2004). Cognitive reserve and the neurobiology of cognitive aging. *Ageing Research Reviews*, *3*, 369-382.

- Zanetti, O., Binetti, G., Magni, E., Rozzini, L., Bianchetti, A., & Trabucchi, M. (1997). Procedural memory stimulation in Alzheimer's disease: Impact of a training programme. *Acta Neurologica Scandinavica*, *95*, 152-157.
- Zanetti, O., Frisoni, G.B., De Leo, D., Dello Buono, M., Bianchetti, A., & Trabucchi, M. (1995). Reality orientation therapy in Alzheimer's disease: Useful or not? A controlled study. *Alzheimer Disease and Associated Disorders*, *9*, 132-138.