

Improving Cognition and Function Through Exercise Intervention in Alzheimer's Disease

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***Purpose:** To analyze the effects of cognition on function and to explore the potential of aerobic exercise for promoting cognitive and functional capacities.*

***Design:** Integrative review of literature.*

***Methods:** Studies were selected based on an extensive search of electronic databases and manual cross-referencing for 1980 to 2006, using the combination of key words: Alzheimer's disease (AD), dementia, or cognitive impairment with function or activities of daily living.*

***Findings:** Three broad themes were identified from the literature analysis. First, global cognition has mainly been used to examine the effect of cognition on function, indicating an assumption that functional decline progresses in a hierarchical manner in AD. Second, specific cognitive domains affect functional decline in different ways. Executive functioning might have more effect on function than does memory. Third, aerobic exercise might promote cognitive and functional capacities in people with AD by modifying neuropathological changes in the brain.*

***Conclusions:** Specific cognitive domains such as executive functioning are important for understanding function in people with AD and are potentially modifiable by aerobic exercise.*

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Functional decline is prevalent and a major contributor to poor healthcare outcomes in people with Alzheimer's disease (AD), the most common type of dementia. Function is defined as the ability to complete major day-to-day activities, including instrumental and basic activities of daily living (IADL and BADL). IADL refers to complex activities such as housekeeping, meal preparation, money management, and shopping; BADL includes self-care activities such as eating, bathing, using the toilet, and dressing (Njegovan, Man-Son-Hing, Mitchell, & Molnar, 2001). Although functional decline has been recognized as necessary for a diagnosis of dementia and is incorporated into several dementia-staging instruments (American Psychiatric Association, 2000; Reisberg & Saeed, 2004) why functional decline occurs is still unclear.

The purpose of this paper is to analyze and synthesize the current scientific evidence for the effects of cognition on function in order to direct the identification and design of nursing interventions. The specific aims of the paper are to: (a) present an integrative review about cognition, its relevant brain structure, and pattern of cognitive impairment in AD, including analysis of the relationship between cognition and functional decline in people with AD and indications for nonpharmacological interventions such as exercise for im-

proving functional independence; (b) discuss the limitations of past research; and (c) propose future research directions grounded in recent advances in neuroscience.

Background

Alzheimer's disease is a progressive and irreversible neurodegenerative disorder characterized by cognitive deficits, including amnesia, apraxia, agnosia, aphasia, and executive dysfunction (American Psychiatric Association, 2000).

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An increasing public health issue, AD is estimated to affect 4.5 million Americans and could afflict 14 million by 2050 (Hebert, Scherr, Bienias, Bennett, & Evans, 2003). About 37% to 49% of community-dwelling people with dementia are functionally dependent (Aguero-Torres, Fratiglioni, Guo, Viitanen, & Winblad, 1998).

Functional decline is a major risk factor for hospitalization (Andrieu et al., 2002), institutionalization (Steeman, Abraham, & Godderis, 1997), and mortality (Newcomer, Covinsky, Clay, & Yaffe, 2003). People with AD have reported that their quality of life deteriorates as their function declines (Włodarczyk, Brodaty, & Hawthorne, 2004), and functional independence is pivotal for them to maintain a continuous sense of self-identity (Phinney, 1998). Functional decline further contributes to healthcare expenditures. People with severe functional decline incur costs 10 times greater than those without such deficits (Taylor, Schenkman, Zhou, & Sloan, 2001). The development of an additional functional disability costs Medicare >\$399 per capita annually (Thomas, 2005). Without appropriate interventions, persons with AD continue to experience irreversible cognitive and functional decline (Green, Mohs, Schmeidler, Aryan, & Davis, 1993). Until AD can be prevented or cured, promoting cognitive and functional capacities in this population remains both a clinical and a research priority and has significant social and practical implications (Steeman et al., 1997).

Studies have shown that nonpharmacological interventions might be effective in delaying functional decline in people with AD. For example, despite their greater degree of functional dependence at baseline, people with cognitive impairment were able to achieve functional gain comparable to people with intact cognition from a comprehensive outpatient rehabilitation program (Yu, Evans, & Sullivan-Marx, 2005). People with mild-to-moderate AD could reduce the amount of time needed for functional performance after receiving a training program designed to stimulate remaining memory skills (Zanetti et al., 1997). An intriguing question arose from those encouraging findings: How do nonpharmacological interventions work? An integrative review about the effects of cognition on function in older adults with AD will help answer this question and facilitate the development and testing of interventions such as exercise to promote functional independence. Pharmacological studies were excluded because current treatments for AD, such as acetylcholinesterase inhibitors, lead to small, limited improvements in cognition and function. Medications do not appear to affect the underlying cause of AD, and they have significant side effects (Areosa Sastre, McShane, & Sherriff, 2004; Birks & Harvey, 2003; Loy & Schneider, 2004).

Methods

Electronic databases (CINAHL, PubMed, and PsycINFO) were searched with the combination of key words: AD, dementia, or cognitive impairment with function or activities of daily living for the period 1980 to 2006. All

citations were entered to an Endnote 6 reference library. After removing duplicates, 1,512 articles remained. Forty-four articles meeting the selection criteria were considered for further review. The inclusion criteria were: (a) diagnosis of probable or possible AD, (b) indication of the relationship between cognition and function, and (c) printed in English. The exclusion criteria were: (a) diagnosis of dementia other than AD, because other dementias have different pathological mechanisms than does AD, and (b) drug studies, for reasons previously mentioned. Manual cross-referencing was performed to identify important references not yielded in the electronic search. Studies meeting selection criteria were assessed independently by two authors (FY and AMK) using the Modified Quality Assessment Criteria (see Table 1; Chalmers, 1987; Meade & Richardson, 1997). Eighteen studies of high quality (a score of ≥ 12) were included for the analysis of the effect of cognition on function, regarding global cognitive impairment (Table 2) and discrete cognitive domain (Table 3).

Findings

Cognition, Its Relevant Brain Structure, and Pattern of Impairment in AD

Cognition and its relevant brain structure. Three specific cognitive domains: memory, executive functioning, and visuospatial functioning, are pertinent to understanding function in AD. Memory includes explicit episodic memory and implicit procedural memory. Explicit episodic memory is defined as a conscious process of recollection of previous events and experiences; implicit memory refers to the memory process that does not require conscious recollection to be activated and re-experienced (Morris, 1996). The hippocampal system is intricately involved in the function of explicit memory; procedural memory can be established through brain mechanisms independent of the hippocampal system (Nadel, Samsonovich, Ryan, & Moscovitch, 2000).

Executive functioning refers to a set of cognitive skills to organize, coordinate, and sequence goal-directed behaviors. It significantly influences the effectiveness of memory and other cognitive processes (Hall, Smith, & Keele, 2001). Executive functioning has three components: (a) working memory: the ability to represent changing information and integrate sensory information with past experience; (b) inhibitory control: the ability to suppress behavior and information not pertinent to the task at hand; and (c) preparatory set: the ability to organize and coordinate goal-directed behavior (Fuster, 1997). Brain regions involved in executive functioning are frontal-cortical and frontal-subcortical circuitry. Working memory, inhibitory control, and preparatory set may be related to dorsolateral, orbital, and anterior cingulate prefrontal cortical regions respectively (Royall et al., 2002).

Visuospatial functioning is the cognitive process of perception, comprehension, and interpretation of visual and spatial information. Visuospatial functioning facilitates efficient and accurate object and face recognition, safe

Table 1. Modified Scale to Assess Quality of Studies

	Yes (2)	Partly Yes(1)	No (0)
1. Was the patient population profile (demographics, residence, referral pattern) well described?			
2. Was the sampling/selection process of persons well characterized? (objective outcome criteria used)			
3. Was there complete follow-up of recruited participants?			
4. Was the adjustment for confounding factors such as dementia, very old age, severe medical illness described?			
5. Was a structured tool/interview used for the definition of cognition, function, behaviors and other risk factors?			
6. Was a structured tool/interview (validated instrument versus DSM or NINCD-ADRD used for diagnosing AD)?			
7. Were raters/interviewers blinded to outcome assessment?			
8. Was a sample size for adequate power and clinically significant associations calculated and stated in the method?			
9. Were statistical methods clearly explained? (e.g., <i>OR</i> and 95% <i>CI</i>)			
Total _____ (range 0-18)			

Note. Modified from Chalmers et al. (1987); and Meade & Richardson (1997).

environmental navigation, and visuomotor skills that underlie skilled movements such as dialing a phone, dressing, and hygiene. The occipitotemporal visual pathways are more prominently associated with visual object recognition, and

the occipitoparietal regions are more frequently involved with spatial perception (Morris, 1996).

Pattern of cognitive impairment in AD. Clinical presentations in AD typically show wide variability because

Table 2. Summary of Studies on the Effect of Cognition on Function: Global Cognitive Impairment

Study	Design	Sample	Main measures	Major findings
Dodge (2003)	10-year prospective epidemiologic	1,201 community-residing adults	CDR, OARS-IADL	People with AD persons spent more absolute years and a greater portion of their remaining life with 6 to 7 IADL impairment.
Drachman (1990)	54-month longitudinal	42 community-dwelling people with AD	Clinical Severity Score, dressing, eating, bathing	Degree of severity predicted subsequent dependence in BADL dressing, eating and bathing and incontinence.
Farias (2003)	Cross-sectional	42 persons with AD from a memory clinic	Neuropsychological battery, IADLS	Memory, attention, visuospatial functioning, language, executive functioning and praxis accounted for 25% of the variance in IADL.
Galasko (1995)	3-year longitudinal	343 community-dwelling people with AD from a CERAD project	MMSE, CDR, BDS	Both dementia severity and rate of cognitive decline influenced IADL and BADL decline. IADL decline precedes BADL. Within each IADL and BADL, a sequential loss occurred.
Green (1993)	Average 31-month longitudinal	104 people with AD from a memory clinic	PSMS, IADLS	IADL and PSMS worsened 2.06-point and 4.44 –point annually on average. Change of IADL was smaller for patients with severe dementia.
Holtzer (2003)	5-year prospective	236 outpatients with AD (14 from nursing home)	MMSE, the Dependence Scale	Fast rate of cognitive decline was associated with greater dependence. High baseline cognition and slow cognitive decline were protective.
Njegovan (2001)	5-year longitudinal	5,874 elders of the Canadian Health and Aging study.	Modified MMSE, OARS	A strong relationship between cognition and function controlling for baseline cognition was found. A hierarchy loss of function: IADL being lost earlier at higher cognition than BADL.
Schmeidler (1998)	1-year prospective	151 AD outpatients patients from a research clinic	ADAS-Cog, IADLS, PSMS	The rate of total IADL scores change greater for patients with moderate and severe AD. The rate of total PSMS change was greater for patients with severe and very severe AD.
Stern (1996)	5-year longitudinal	236 outpatients with AD	Modified MMSE, BDRS	IADL declined more rapidly earlier in AD. BADL had a slow linear decline as AD progressed into moderate to severe stages.
Suh (2004)	1-year longitudinal	107 community residing people with AD	ADAS-cog, MMSE, DAD	The average annual decline in DAD was 15.1 pts. IADL showed linear decline. BADL decline did not happen until moderate to severe stages.

Table 3. Summary of Studies on the Effect of Cognition on Function: Discreet Cognitive Domain

Boyle (2003)	Cross-sectional	45 AD outpatients from a memory clinic	DRS, FrSBel, ADL	Executive dysfunction explained 9% of variance in BADL and 17% of variance in IADL.
Edwards (1991)	Cross-sectional	142 AD, 113 control from a memory and aging project.	Constructional apraxia, Katz ADL, SPMSQ	Constructional apraxia was related to Katz: total, bathing, dressing, toileting, and incontinence in moderate dementia, and related to dressing in mild dementia.
Liu (2004)	Cross-sectional	20 AD outpatients and 21 control	Attention test, DAD	Patients with AD experienced visuospatial attention deficits, but visuospatial neglect did not affect function.
Perry (2000)	Cross-sectional	24 AD outpatients and 2 control (44 and 33 each), UK	Progressive deterioration scale for function	No significant correlation between episodic memory and function. Visuospatial functioning was the sole cognitive predictor for function.
Royall (2000)	Cross-sectional	561 retirees living in a retirement community	MMSE, EXIT25, CLOX, IADL	Executive dysfunction contributed negatively to IADL even after controlling for MMSE and age.
Royall (2005)	3-year longitudinal	547 noninstitutionalized people aged 70 or older	EXIT25, IADL	The rate of change in executive function was independently associated with IADL, even after controlling for age, comorbidity, baseline EXIT25, IADL, and level of care.
Swanberg (2004)	Retrospective analysis over 1 year	131 AD patients from tertiary referral centers, 64 control	ADAS-cog expanded, the AD Cooperative Study ADL Inventory	64% of patients with AD had executive dysfunction and performed worse on functional test over a year.
Venable (1991)	Cross-sectional	19 pairs of AD patient/caregivers (4 pair from nursing home)	CDR, TDS, TPT, IADLS, PSMS	Temporal disorganization and difficulty with tracking time passage affected the abilities of elders with AD to carry out both IADL and BADL, with a stronger effect on BADL.

Note. ADAS = Alzheimer's Disease Assessment Scale; ADL questionnaire or scale (Lawton and Brody); BDRS or BDS = Blessed Dementia Rating Scale; CDR = Clinical Dementia Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CLOX = Executive Clock Drawing Test; EXIT25 = Executive Interview 25; DAD = Disability Assessment for Dementia Scale; FrSBel = Frontal Systems Behavioral Inventory; Function = IADL and BADL together; IADLS = Instrumental Activities of Daily Living Scale; MMSE = Mini-Mental State Examination; OARS = Older Americans Resources and Services; PSMS = Physical Self-Maintenance Scale; SPMSQ = Short Portable Mental Status Questionnaire; TDS = Temporal Disorganization Scale; TPT = Test of Time Passage.

brain regions are differently affected by AD neuropathological changes (β -amyloid plaques and neurofibrillary tangles). Although memory loss is the most frequent early symptom and is considered a hallmark of AD, deficits in other cognitive domains such as executive or visuospatial functioning can be the dominant presenting symptoms. Subtle executive dysfunction might occur earlier than does memory loss, but it is not easily recognized in office or clinic settings or even by family members (Rapp & Reischies, 2005). Several studies have indicated the early occurrence of executive dysfunction in AD and its persistence throughout the disease trajectory (Morris, 1996; Price et al., 1993). The prevalence of executive dysfunction in people with AD is 64% with a 1-year incidence rate of 34% (Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). Although memory loss remains the hallmark clinical symptom of AD, not all cognitive domains decline at the same rate or in a similar pattern, as indicated in psychometric assessments for specific aspects of cognition (Matsuda & Saito, 2005).

Relationship Between Cognition and Function in Persons With AD

Global cognitive impairment and functional decline. A common practice in AD research has been to examine the effect of global cognitive impairment on functional decline. Global cognitive impairment is the magnitude of overall cognitive deficits exhibited by a person with AD (Reisberg & Saeed, 2004). Standardized measures of global cognitive im-

pairment, such as the Alzheimer's Disease Assessment Scale, have served three main purposes in research. First, they have high sensitivity for detecting clinical symptoms, which is important given the wide variability of presenting cognitive symptoms of AD. Second, their total scores have been helpful to stage AD severity. Third, the concept of global cognitive impairment has facilitated description of the pattern of functional decline in people with AD.

Research findings have converged to show that global cognitive impairment is related to functional decline. Studies indicated that IADL decline began in mild stages of AD and preceded BADL decline (Galasko et al., 1995; Holtzer et al., 2003). Global cognitive impairment accounted for 25% to 50% of IADL variance (Farias, Harrell, Neumann, & Houtz, 2003). More difficult IADL tasks, such as remembering lists, were lost earlier than were over-learned tasks, such as finding one's way indoors (Galasko et al., 1995). As dementia progressed to severe stages, people with AD lost the capacity to perform IADL completely (Green, Mohs, Schmeidler, Aryan, & Davis, 1993; Schmeidler, Mohs, & Aryan, 1998; Stern et al., 1996). Thus, they suffered more years with IADL impairment (Dodge, Shen, Pandav, DeKosky, & Ganguli, 2003). BADL decline was not evident until moderate to severe stages of AD (Green et al., 1993; Njegovan et al., 2001; Stern et al., 1996; Suh, Ju, Yeon, & Shah, 2004). Dressing ability was lost earlier than was toilet use, which in turn preceded feeding and ambulation loss (Galasko et al., 1995; Reisberg, Franssen,

Souren, Auer, & Kenowsky, 1998; Sclan & Reisberg, 1992). BADL decline was a slow process over 10 years (Stern et al., 1996). BADL and IADL declines overlapped during moderate to severe stages of AD (Njegovan et al., 2001). As a complement to measures of global cognitive impairment, functional decline has been incorporated into the staging of AD, e.g., the Functional Assessment Staging (Reisberg & Saeed, 2004).

Using AD diagnosis to predict functional decline was another common practice. The diagnosis was typically made according to standardized diagnostic criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association or in the Diagnostic and Statistical Manual for Mental Disorders DSM-IV-TRTM (American Psychiatric Association, 2000). An AD diagnosis was found to increase the likelihood of BADL dependence at baseline and to contribute to greater BADL decline over time (Drachman, O’Donnell, Lew, & Swearer, 1990).

Memory and function. Despite decades of work on quantifying memory and explaining functional decline in the context of memory impairment, studies directly focused on the relationship between memory and function are limited. Some studies have shown the association between explicit memory and IADL (Galasko et al., 1995; Nadel et al., 2000), while others challenged the existence of such a link (Perry & Hodges, 2000). The progression of memory deficits from explicit memory to procedural memory theoretically explains the pattern of functional decline from IADL to BADL. In other words, when deficits in explicit episodic memory become apparent, IADL decline occurs because explicit episodic memory provides specific situational and contextual information for effective IADL performance. Implicit procedural memory remains normal until late stages of AD, which might account for the late onset of BADL decline. An intervention study based on this theory showed that people with mild-to-moderate AD could reduce the time needed for functional performance by using a training program designed to stimulate procedural memory (Zanetti et al., 1997).

Executive functioning and function. Executive functioning has been identified as a robust cognitive predictor for functional decline in older adults (Royall, Chiodo, & Polk, 2000). Executive dysfunction independently explained 43% of the IADL variance, while MMSE, demographic characteristics, physical health status, and the number of medications prescribed together explained only an additional 14% in older retirees without a dementia diagnosis (Royall et al., 2000). Executive dysfunction was further found to mediate the association between memory and IADL in community-dwelling older adults without a dementia diagnosis (Royall, Palmer, Chiodo, & Polk, 2005). People with AD who had executive dysfunction experienced greater functional decline than did those without executive dysfunction (Swanberg et al., 2004). Executive dysfunction explained about 17% of IADL variance and 9% of BADL variance in people with AD (Boyle et al., 2003; Venable & Mitchell, 1991).

Visuospatial functioning and function. Findings regarding the effect of visuospatial functioning on function are inconsistent due partly to measurement and methodologic limitations. Visuospatial dysfunction was the only cognitive predictor of functional decline in one study (Perry & Hodges, 2000), but results of another study were contradictory to this finding (Liu, McDowd, & Lin, 2004). Constructional apraxia, i.e., difficulty in assembling discrete components into multidimensional designs, appears related to greater difficulty in dressing in people with mild AD, and in activities such as meal preparation, dressing, and hygiene in people with moderate AD (Edwards, Baum, & Deuel, 1991). Studies with well-defined and ecologically valid measures are especially needed to investigate these possible relationships.

In summary, both global cognitive impairment and the rate of global cognitive decline affect function in AD. Although a valuable concept, global cognition does not elucidate which discrete cognitive domains contribute to specific functional decline and which underlying brain mechanisms are involved in such an effect. Because the clinical presentation of AD can be variable and is neither global nor diffuse in nature, emphasis on discrete cognitive domains might be the key to understanding and predicting an individual’s specific pattern of functional ability and functional decline.

Nonpharmacological Interventions for Improving Functional Independence

The analysis of the relationship of cognition and function shows that interventions targeting specific cognitive domains such as executive functioning could delay functional decline in people with AD. Aerobic exercise is such an intervention. Aerobic exercise refers to exercises that involve continuous and rhythmic use of large muscles for at least 15 minutes three or more times per week and increase resting heart rate by at least 60% of heart rate reserve (American College of Sports Medicine, 2002). Neuroscience breakthroughs in AD research have shown that aerobic exercise delays β -amyloid accumulation in transgenic mice genetically engineered to exhibit AD neuropathological changes. The performance of aerobic exercise by mice improved memory and learning (Adlard, Perreau, Pop, & Cotman, 2004; Lazarov et al., 2005). Aerobic exercise stimulates gene expressions of nerve growth factors important for neurogenesis, production and function of neurotransmitters, and synaptogenesis, especially in the hippocampal region where AD pathology is severe (Hall, Smith, & Keele, 2001; Jernigan et al., 2001; Kramer et al., 1999; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). In older adults without AD, aerobic exercise spares brain tissue loss and increases cerebral vasculature and blood flow in frontal, parietal, and temporal cortices (Kramer, Bherer, Colcombe, Dong, & Greenough, 2004). In a recent meta-analysis, older adults without AD achieved a striking improvement in executive functioning

after participation in aerobic exercise (Colcombe & Kramer, 2003).

By logical extension, people with AD might improve their executive functioning by participating in aerobic exercise. Improvements in executive functioning might, in turn, delay functional decline, in addition to its effects on improving endurance and stamina. To date, studies focused on aerobic exercise in people with AD are limited and vary greatly in the exercise programs tested and outcome measures used. Virtually no data are available on the effect of aerobic exercise on specific cognitive domains. Two studies indicated that people with AD who bicycled 20 minutes three times a week for 3 months or walked 30 minutes daily for 7 weeks realized gains in global cognition and attention and did not show functional decline (Palleschi et al., 1996; Rolland et al., 2000). Additionally, exercise programs have been effective in improving a variety of health outcomes in people with AD, e.g., endurance, strength, and duration of exercise participation (Arkin, 2003), behavioral symptoms, sleep disorders, days with restricted activities, rate of institutionalization, and the use of hypnotic medications (Landi, Russo, & Bernabei, 2004; Teri et al., 2003).

Nonaerobic exercises, such as weight training, have also shown some cognitive benefits when combined with aerobic exercise or used alone (Heyn, Abreu, & Ottenbacher, 2004). However, the mechanisms for such effects are unclear and might not operate through the same cerebral mechanisms as aerobic exercise. Other interventions, e.g., cognitive rehabilitation, could also improve cognition and function (Avila et al., 2004; Zanetti et al., 1997). However, a meta-analysis of cognitive rehabilitation showed that the cognitive and functional benefits were inconsistent and small (Clare, Woods, Moniz Cook, Orrell, & Spector, 2004).

To summarize, studies on the effectiveness of physical exercise in community-dwelling people with AD generally have small sample sizes, variable exercise regimes, and inconsistent outcome measures. The emerging data, however, are promising and indicate an important direction for further research.

Limitations of Past Research

Global cognitive impairment has long been a key construct in AD research. Nevertheless, reliance on this construct significantly limits the advancement of further knowledge in five ways. First, global cognitive impairment does not account for individual patterns of cognitive impairment and remaining cognitive capacity. This is particularly important because the clinical presentation of AD is highly variable. Second, not all cognitive domains affect functional decline. The effects of some cognitive domains might be mediated by a confounder such as unmeasured executive functioning. Third, global cognitive impairment is not a well-defined cognitive target for interventions. Fourth, measures for global cognitive impairment usually do not include assessment of

executive functioning. Fifth, emphasizing global features of cognition might mask significant variations in treatment responsiveness.

Over the past 2 decades, the exponential increase in knowledge in neuropsychology has significantly advanced understanding of human cognition. For example, the quantification of executive functioning began to unveil the role of this cognitive domain in affecting IADL and BADL in people with AD (Swanberg et al., 2004). However, function is still being explained mainly in the context of memory impairment, which also has been inadequately studied.

Furthermore, neuroscience breakthroughs in AD research have not been translated into clinical intervention studies. Studies examining the effects of aerobic exercise on cognition and function are limited. Although many studies have been focused on the effectiveness of cognitive rehabilitation on cognition and function, they mainly pertain to memory, but not to other cognitive domains that are pivotal to functional independence.

Implications for Future Research

Studies to elucidate the extent to which IADL and BADL depend on various cognitive domains are necessary for understanding functional decline and developing more appropriate and feasible individualized interventions for people with AD. For example, testing the relationships of episodic memory, procedural memory, and executive functioning with function, using ecologically valid instruments, are needed.

Knowledge advances in neuropsychology and neuroscience have significant implications for further nursing research on AD. Aerobic exercise holds great promise as a nonpharmacological intervention for improving cognition and function. Despite the long-recognized health benefits of aerobic exercise, its effect on delaying the progression of cognitive and functional decline is just beginning to be adequately studied. Other domains of function such as social and emotional function are relevant to cognition and might be appropriate outcomes of nursing interventions aiming at improving cognition. Additionally, other nonpharmacological interventions, e.g., rehabilitation for executive functioning, require further development and testing for their effectiveness on delaying functional decline in people with AD. Those nonpharmacological interventions are part of nursing practice and important areas of nursing research.

With the increasing use of neuroimaging techniques such as functional magnetic resonance imaging and positron emission topography, researchers can observe directly the effects of aerobic exercise on cognition and brain plasticity in AD. An important next step in research, therefore, is to examine the effectiveness of aerobic exercise on brain structure and function and to establish clinical practice guidelines regarding the type and dosage of aerobic exercise necessary to produce and maintain those benefits.

Conclusions

Although functional impairment remains a core diagnostic feature of AD, the effects of cognitive domains on functional decline are not fully understood. This integrative review indicates that specific cognitive domains have important effects on delaying functional decline. Interventions to improve specific cognitive domains have the potential for delaying functional decline in people with AD.

References

- Adlard, A.P., Perreau, V.M., Pop, V., & Cotman, C.W. (2004). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience*, 25, 217–221.
- Aguero-Torres, H., Fratiglioni, L., Guo, Z., Viitanen, M., & Winblad, B. (1998). Prognostic factors in very old demented adults: A seven-year follow-up from a population-based survey in Stockholm. *American Journal of Public Health*, 46(4), 444–452.
- American College of Sports Medicine. (2002). *Guidelines for graded exercise testing and exercise prescription*. Philadelphia: Lea and Febiger.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed.), text revision (DSM-IV-TRTM). Washington, DC: Author.
- Andrieu, S., Reynish, E., Nourhashemi, F., Shakespeare, A., Moulias, S., Ousset, P.J., et al. (2002). Predictive factors of acute hospitalization in 134 patients with Alzheimer's disease: A one year prospective study. *International Journal of Geriatric Psychiatry*, 17(5), 422–426.
- Areosa Sastre, A., McShane, R., & Sherriff, F. (2004). Memantine for dementia. *Cochrane Database of Systematic Reviews*, 4.
- Arkin, S.M. (2003). Student-led exercise sessions yield significant fitness gains for Alzheimer's patients. *American Journal of Alzheimer's Disease & Other Dementias*, 18(3), 159–170.
- Avila, R., Bottino, C.M., Carvalho, I.A., 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(11), 1721–1729.
- Birks, J.S., & Harvey, R. (2003). Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Systematic Reviews*, 3.
- Boyle, P.A., Malloy, P.F., Salloway, S., Cahn-Weiner, D.A., Cohen, R., & Cummings, J.L. (2003). Executive dysfunction and apathy predict functional impairment in Alzheimer disease. *American Journal of Geriatric Psychiatry*, 11(2), 214–221.
- Chalmers, T.C., Levin, H., Sacks, H.S., Reitman, D., Berrier, J., & Nagalingam, R. (1987). Meta-analysis of clinical trials as a scientific discipline I: Control of bias and comparison with large co-operative trials. *Statistics in Medicine*, 6, 315–328.
- Clare, L., Woods, R.T., Moniz Cook, E.D., Orrell, M., & Spector, A. (2004). Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *Cochrane Database of Systematic Reviews*, 4.
- Colcombe, S.J., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science*, 14, 125–130.
- Dodge, H.H., Shen, C., Pandav, R., DeKosky, S.T., & Ganguli, M. (2003). Functional transitions and active life expectancy associated with Alzheimer Disease. *Archives of Neurology*, 60, 253–259.
- Drachman, D.A., O'Donnell, B.F., Lew, R.A., & Swearer, J.M. (1990). The prognosis in Alzheimer's disease. 'How far' rather than 'how fast' best predicts the course. *Archives of Neurology*, 47(8), 851–856.
- Edwards, D.F., Baum, C.M., & Deuel, R.K. (1991). Constructional apraxia in Alzheimer's disease: Contributions to functional loss. In E.D. Taira (Ed.), *The mentally impaired elderly: Strategies and interventions to maintain function* (2nd ed.; pp. 53–68). Binghamton, NY: Haworth Press.
- Farias, S.T., Harrell, E., Neumann, C., & Houtz, A. (2003). The relationship between neuropsychological performance and daily functioning in individuals with Alzheimer's disease: Ecological validity of neuropsychological tests. *Archives of Clinical Neuropsychology*, 18(6), 655–672.
- Fuster, J. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the executive lobe* (2nd ed.). New York: Lippincott-Raven Press.
- Galasko, D., Edland, S.D., Morris, J.C., Clark, C., Mohs, R., & Koss, E. (1995). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part XI. Clinical milestones in patients with Alzheimer's disease followed over 3 years. *Neurology*, 45(8), 1451–1455.
- Green, C.R., Mohs, R.C., Schmeidler, J., Aryan, M., & Davis, K.L. (1993). Functional decline in Alzheimer's disease: A longitudinal study. *Journal of the American Geriatrics Society*, 41(6), 654–661.
- Hall, C.D., Smith, A.L., & Keele, S.W. (2001). The impact of aerobic activity on cognitive function in older adults: A new synthesis based on the concept of executive control. *European Journal of Cognitive Psychology*, 13(1/2), 279–300.
- Hebert, L.E., Scherr, P.A., Bienias, J.L., Bennett, D.A., & Evans, D.A. (2003). Alzheimer disease in the US population: Prevalence estimates using the 2000 census. *Archives of Neurology*, 60(8), 1119–1122.
- Heyn, P., Abreu, B.C., & Ottenbacher, K.J. (2004). The effects of exercise training on elderly persons with cognitive impairment and dementia: A meta-analysis. *Archives of Physical Medicine and Rehabilitation*, 85(10), 1694–1704.
- Holtzer, R., Wegesin, D.J., Albert, S.M., Marder, K., Bell, K., Albert, M., et al. (2003). The rate of cognitive decline and risk of reaching clinical milestones in Alzheimer disease. *Archives of Neurology*, 60(8), 1137–1142.
- Jernigan, T.L., Archibald, S.L., Fennema-Notestine, C., Gamst, A.C., Stout, J.C., Bonner, J., et al. (2001). Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiological Aging*, 22(4), 581–594.
- Kramer, A.F., Hahn, W., Cohen, N.J., Banich, M.T., McAuley, E., Harrison, C.R., et al. (1999). Ageing, fitness and neurocognitive function. *Nature*, 400(6743), 418–419.
- Kramer, A.K., Bherer, L., Colcombe, S.J., Dong, W., & Greenough, W.T. (2004). Environmental influences on cognitive and brain plasticity during aging. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, 59, M940–M957.
- Landi, F., Russo, A., & Bernabei, R. (2004). Physical activity and behavior in the elderly: A pilot study. *Archives of Gerontology and Geriatrics*, 9(Suppl.), 235–241.
- Lazarov, O., Robinson, J., Tang, Y.P., Hairston, I.S., Korade-Mirnic, Z., Lee, V.M., et al. (2005). Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell*, 120(5), 701–713.
- Liu, C.J., McDowd, J., & Lin, K.C. (2004). Visuospatial inattention and daily life performance in people with Alzheimer's disease. *American Journal of Occupational Therapy*, 58(2), 202–210.
- Loy, C., & Schneider, L. (2004). Galantamine for Alzheimer's disease. *Cochrane Database of Systematic Reviews*, 4.
- Matsuda, O., & Saito, M. (2005). Functional competency and cognitive ability in mild Alzheimer's disease: Relationship between ADL assessed by a relative/carer-rated scale and neuropsychological performance. *International Psychogeriatrics*, 17(2), 275–288.
- Meade, M.O., & Richardson, W.S. (1997). Selecting and appraising studies for a systematic review. *Annals of Internal Medicine*, 127, 531–537.
- Morris, R.G. (1996). *The cognitive neuropsychology of Alzheimer-type dementia*. New York: Oxford University Press.
- Nadel, L., Samsonovich, A., Ryan, L., & Moscovitch, M. (2000). Multiple trace theory of human memory: Computational, neuroimaging, and neuropsychological results. *Hippocampus*, 10(4), 352–368.
- Newcomer, R., Covinsky, K.E., Clay, T., & Yaffe, K. (2003). Predicting 12-month mortality for persons with dementia. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, 58(3), S187–S198.
- Njegovan, V., Man-Son-Hing, M., Mitchell, S.L., & Molnar, F.J. (2001). Hierarchy of functional loss associated with cognitive decline in older persons. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 10, M638–M643.
- Palleschi, L., Vetta, F., De Gennaro, E., Idone, G., Scottosanti, G., Gianni, W., et al. (1996). Effect of aerobic training on the cognitive performance of elderly patients with senile dementia of Alzheimer type. *Archives of Gerontology and Geriatrics*, 5, 47–50.

- Perry, R.J., & Hodges, J.R. (2000). Relationship between functional and neuropsychological performance in early Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 14(1), 1–10.
- Phinney, A. (1998). Living with dementia from the patient's perspective. *Journal of Gerontological Nursing*, 24(6), 8–15.
- Price, B.H., Gurvit, H., Weintraub, S., Geula, C., Leimkuhler, E., & Mesulam, M. (1993). Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. *Archives of Neurology*, 50(9), 931–937.
- Rapp, M.A., & Reischies, F.M. (2005). Attention and executive control predict Alzheimer disease in late life: Results from the Berlin Aging Study (BASE). *American Journal of Geriatric Psychiatry*, 13(2), 134–141.
- Reisberg, B., Franssen, E.H., Souren, L.E., Auer, S., & Kenowsky, S. (1998). Progression of Alzheimer's disease: Variability and consistency: Ontogenic models, their applicability and relevance. *Journal of Neural Transmission*, 54(Suppl.), 9–20.
- Reisberg, B., & Saeed, M.U. (2004). Alzheimer's disease. In J. Sadavoy, L.F. Jarvik, G.T. Grossberg, & B.S. Meyers (Eds.), *Comprehensive textbook of geriatric psychiatry* (3rd ed.). New York: Norton.
- Rolland, Y., Rival, L., Pillard, F., Lafont, C., Rivere, D., Albaredo, J., et al. (2000). Feasibility of regular physical exercise for patients with moderate to severe Alzheimer disease. *Journal of Nutrition, Health & Aging*, 4(2), 109–113.
- Royall, D.R., Chiodo, L.K., & Polk, M.J. (2000). Correlates of disability among elderly retirees with 'subclinical' cognitive impairment. *Journals of Gerontology Series A Biological Sciences and Medical Sciences*, 55(9), M541–M546.
- Royall, D.R., Lauterbach, E.C., Cummings, J.L., Reeve, A., Rummans, T.A., Kaufer, D.I., et al. (2002). Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14(4), 377–405.
- Royall, D.R., Palmer, R., Chiodo, L.K., & Polk, M.J. (2005). Executive control mediates memory's association with change in instrumental activities of daily living: The Freedom House Study. *Journal of the American Geriatrics Society*, 53, 11–17.
- Schmeidler, J., Mohs, R.C., & Aryan, M. (1998). Relationship of disease severity to decline on specific cognitive and functional measures in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 12(3), 146–151.
- Sclan, S.G., & Reisberg, B. (1992). Functional assessment staging (FAST) in Alzheimer's disease: Reliability, validity, and ordinality. *International Psychogeriatrics*, 4(Suppl. 1), 55–69.
- Steeman, E., Abraham, I., & Godderis, J. (1997). Risk profiles for institutionalization in a cohort of elderly people with dementia or depression. *Archives of Psychiatric Nursing*, 11(6), 295–303.
- Stern, Y., Liu, X., Albert, M., Brandt, J., Jacobs, D.M., Del Castillo-Castaneda, C., et al. (1996). Application of a growth curve approach to modeling the progression of Alzheimer's disease. *Journal of Gerontology Series A Biological, Sciences and Medical Sciences*, 51(4), M179–M184.
- Suh, G.H., Ju, Y.S., Yeon, B.K., & Shah, A. (2004). A longitudinal study of Alzheimer's disease: Rates of cognitive and functional decline. *International Journal of Geriatric Psychiatry*, 19(9), 817–824.
- Swanberg, M.M., Tractenberg, R.E., Mohs, R., Thal, L.J., & Cummings, J.L. (2004). Executive dysfunction in Alzheimer disease. *Archives of Neurology*, 61(4), 556–560.
- Taylor, D.H. Jr., Schenkman, M., Zhou, J., & Sloan, F.A. (2001). The relative effect of Alzheimer's disease and related dementias, disability, and comorbidities on cost of care for elderly persons. *Journal of Gerontology. Series B, Psychological Sciences and Social Sciences*, 56(5), S285–S293.
- Teri, L., Gibbons, L.E., McCurry, S.M., Logsdon, R.G., Buchner, D.M., Barlow, W.E., et al. (2003). Exercise plus behavioral management in patients with Alzheimer disease: A randomized controlled trial. *JAMA*, 290(15), 2015–2022.
- Thomas, V.S. (2005). Restoring success where once was thought only failure lay: The viability of functional rehabilitation for people with cognitive impairment. *Journal of the American Geriatrics Society*, 53, 1624–1626.
- Venable, S.D., & Mitchell, M.M. (1991). Temporal adaptation and performance of daily living activities in persons with Alzheimer's disease. *Physical and Occupational Therapy in Geriatrics*, 9(3/4), 31–51.
- Wlodarczyk, J.H., Brodaty, H., & Hawthorne, G. (2004). The relationship between quality of life, mini-mental state examination, and the instrumental activities of daily living in patients with Alzheimer's disease. *Archives of Gerontology and Geriatrics*, 39(1), 25–33.
- Yu, F., Evans, L., & Sullivan-Marx, E. (2005). Functional outcomes for elders with cognitive impairment in a comprehensive outpatient rehabilitation facility. *Journal of the American Geriatrics Society*, 53(9), 1599–1606.
- 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(3), 152–157.