The Link Between Physical Activity and Cognitive Dysfunction in Alzheimer Disease

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Alzheimer disease (AD) is a primary cause of cognitive dysfunction in the elderly population worldwide. Despite the allocation of enormous amounts of funding and resources to studying this brain disorder, there are no effective pharmacological treatments for reducing the severity of pathology and restoring cognitive function in affected people. Recent reports on the failure of multiple clinical trials for AD have highlighted the need to diversify further the search for new therapeutic strategies for cognitive dysfunction. Thus, studies detailing the neuroprotective effects of physical activity (PA) on the brain in AD were reviewed, and mechanisms by which PA might mitigate AD-related cognitive decline were explored. A MEDLINE database search was used to generate a list of studies conducted between January 2007 and September 2014 (n=394). These studies, along with key references, were screened to identify those that assessed the effects of PA on AD-related biomarkers and cognitive function. The search was not limited on the basis of intensity, frequency, duration, or mode of activity. However, studies in which PA was combined with another intervention (eg, diet, pharmacotherapeutics, ovariectomy, cognitive training, behavioral therapy), and studies not written in English were excluded. Thirty-eight animal and human studies met entry criteria. Most of the studies suggested that PA attenuates neuropathology and positively affects cognitive function in AD. Although the literature lacked sufficient evidence to support precise PA guidelines, convergent evidence does suggest that the incorporation of regular PA into daily routines mitigates AD-related symptoms, especially when deployed earlier in the disease process. Here the protocols used to alter the progression of AD-related neuropathology and cognitive decline are highlighted, and the implications for physical therapist practice are discussed.

Alzheimer disease (AD) is a chronic, neurodegenerative disorder that adversely affects neurons in the brain, ultimately resulting in loss of memory and language, behavioral disturbances, and dependence on caregivers. The strongest risk factor for AD is aging, and the risk doubles every 5 years after the age of 65 years.[1] Increasing population, longevity, and economic prosperity have contributed to concern about a dementia epidemic in the aging population. Currently, 26 million people are affected by AD worldwide; the number of affected people is expected to approximate 106 million by the year 2050, provoking serious clinical, social, ethical, and economic problems.[1]

The gradual decline in brain functioning caused by AD has been associated with several characteristic features, including changes in synaptic number and function, neurogenesis, and neurotrophin levels, plaques and neurofibrillary tangles (NFTs), and abnormal circadian rhythms.[2] The progression of these features is considered critical to the development of impairments in cognition, defined here as the unique combination of attention, learning, memory, language, visuospatial skills, and executive function.[3] Notably, many pathological features precede AD-related cognitive decline by decades,[4] prompting the notion that there is ample time to mitigate symptom progression. However, despite the window of opportunity, currently available pharmacotherapies (eg, donepezil HCl [Aricept, Eisai Co Ltd, Tokyo, Japan], galanthamine HBr [Razadyne, Janssen Pharmaceuticals Inc, Beerse, Belgium], rivastigmine tartrate [Exelon, Novartis Pharmaceuticals Corp, Basel, Switzerland], and memantine HCl [Namenda, Forest Laboratories Inc, New York, New York]) offer transient symptomatic relief only.[5] Given the lack of disease-modifying options,[6] it is imperative to diversify the search for feasible and effective interventions.[7] This realization has prompted great interest in the use of physical activity (PA) to attenuate the severity of neuropathological features associated with cognitive decline in AD.

Physical activities are those that require energy expenditure and involve bodily movements produced by skeletal muscles.[8] Physical exercise has been defined as a subcategory of PA that connotes purposeful, planned, and structured endeavors undertaken to improve skill or physical fitness level.[8] Convergent evidence suggests that PA can alter the progression of AD-related neuropathology and cognitive decline,[9–11] leading to the incorporation of PA into basic clinical management protocols for AD.[1] Because it is important that physical therapists understand the means by which PA can be beneficial, from both self-education and patient education perspectives, the aims of this review are to discuss key features of AD pathology, explore the putative mechanisms by which PA might mitigate these features, review protocols used to effectuate the positive effects of PA on AD in both animal and clinical studies, and highlight implications for physical therapists.

Pathological Features of AD

Amyloid plaques and NFTs are characteristic features of AD. Amyloid plaques comprise a potentially toxic protein called amyloid beta (Aβ).[12] In AD, the plaques are heterogeneously interspersed throughout the brain.[12] Neurofibrillary tangles are abnormal forms of twisted protein threads found inside axons and comprising insoluble tau.[13] For many years, it has been thought that plaques and NFTs may cause the neuronal damage seen in AD. However, such an overly simplistic concept has yielded to contemporary conceptualizations in which AD is viewed as a multifactorial disease arising from several abnormal complex features and processes (Fig. 1).

We systematically reviewed how PA might be deployed to alter the more salient features of AD and, in turn, mitigate cognitive decline. Infused in this discussion is an integration of data derived from both rodent and human studies. This "mixed presentation" is necessary given the obvious limits for experimental manipulation of brain tissue in living humans. Admittedly, evidence from rodents is not a substitute for human studies. Rather, the aim of rodent investigations is to generate preclinical data to expedite the pace of discovery, bolster epidemiological research, and bridge the temporal lag between knowledge creation and clinical trials. With this caveat in mind, we present a mixture of convergent data suggesting that PA benefits brain function and cognition in AD.

This review was designed and conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[14]

Search Procedures

In an attempt to capture relevant data, we conducted a computer-based search of MEDLINE and performed manual searches of key references to identify studies that investigated the effect of PA on the brain in AD and putative mechanisms by which PA might mitigate cognitive decline in AD.

Key word search criteria combined the terms "Alzheimers" and "exercise." This search was used to generate a list of relevant studies conducted between January 2007 and September 2014 (n=394).

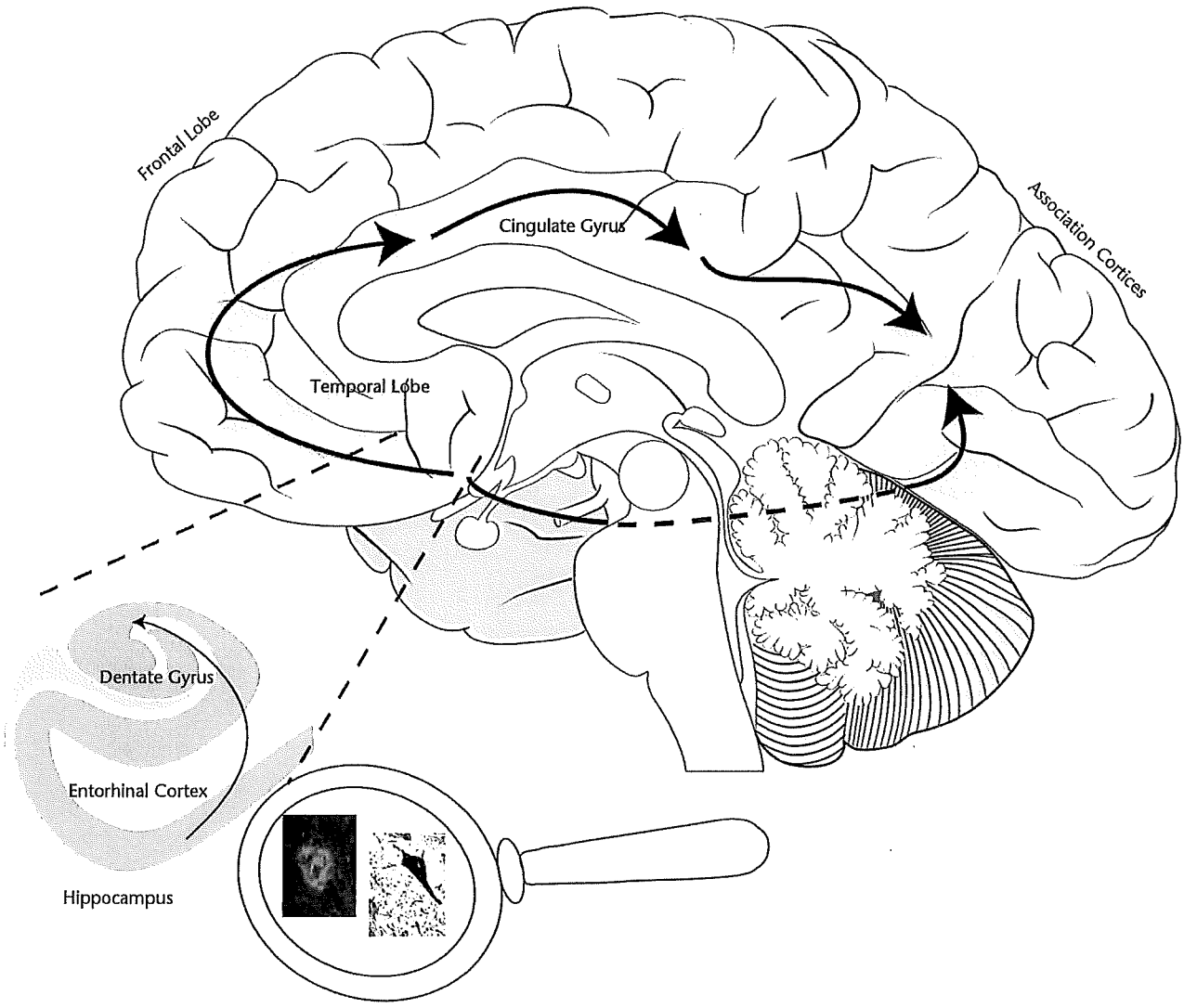

Figure 1.
Sagittal view of the human brain depicting the progression of Alzheimer disease (AD) pathology. Plaques and tangles appear first in the entorhinal cortex and hippocampus before spreading toward other brain regions. The behavioral manifestations of AD reflect the degree of progression of AD pathology to various brain regions. Thus, hippocampus-dependent functions, such as spatial learning and short-term memory, are affected early in the course of disease, but motor functions are affected much later.

Selection Criteria

Peer-reviewed intervention studies that assessed the effects of exercise on characteristic features associated with AD and cognitive decline were included in the present review. No restrictions were placed on intensity, frequency, duration, or mode of intervention. However, multifactorial studies that combined exercise with other interventions (eg, diet, pharmacotherapeutics, ovariectomy, cognitive training, or behavioral therapy) were excluded, as were studies not written in English.

Data Abstraction

Literature searches and data abstraction were conducted independently by one investigator using a standardized template and confirmed by 2 other reviewers. Disagreements were resolved by discussion among the investigators until consensus was reached.

Evidence Synthesis

Figure 2 shows an overview of study flow. Information pertaining to participants, study characteristics, biomedical measurements, and cognition was extracted with an unmasked standardized method as described above. Tables 1 and 2 show summaries of study characteristics and findings, organized by animal and human studies.

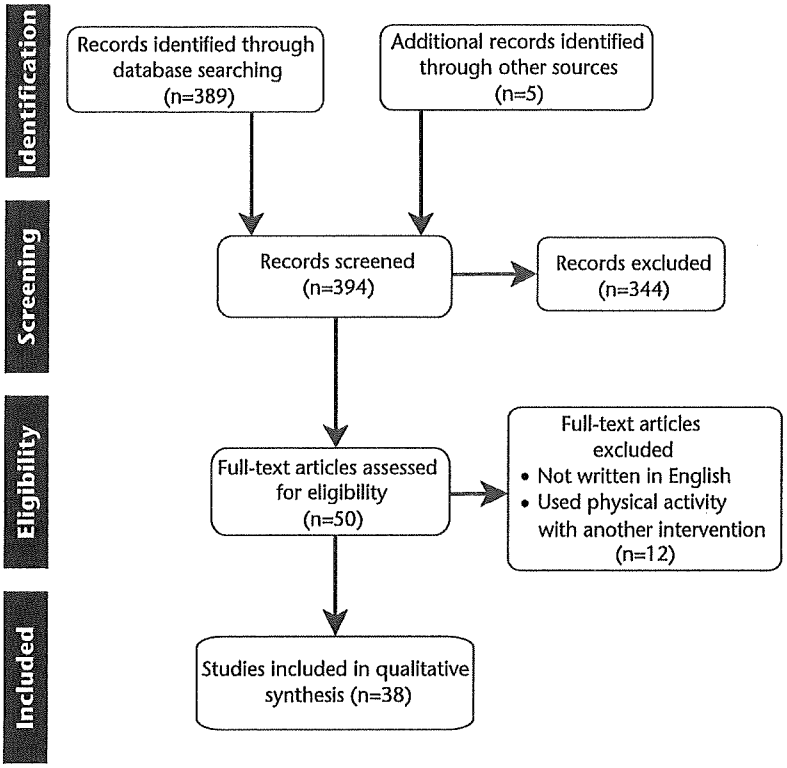

Figure 2.
Schematic representation of procedures used to identify, screen, and select studies for review. The MEDLINE database was searched with the key words "exercise" and "Alzheimers." Studies were excluded from this review for the following reasons: they were not intervention studies, they failed to assess Alzheimer disease–related biomarkers of cognitive function, they combined exercise with other interventions, and they were not written in English.

Putative Effects of PA on Aβ Production and Accumulation

A characteristic feature of AD is the accumulation of amyloid plaques in the brain.[12] The accumulation of Aβ is thought to result from increased production or reduced clearance of this molecule (or both). It has been shown that mutations and polymorphisms in genes—such as those for amyloid precursor protein (APP), presenilins 1 and 2, apolipoprotein E, and sortilin-related receptor 1—result in increased accumulation of Aβ, failure of clearance mechanisms, and formation of amyloid plaques.[13,15] Amyloid plaque formation is problematic because the accumulation of amyloid plaques is believed to trigger a cascade of events that lead to dysfunction and death of neighboring neurons.[16,17] Knowledge of the adverse effects of Aβ has led to the hypothesis that a reduction in harmful Aβ accumulation might prevent neuronal degeneration, especially in people at high risk for AD.[5]

Accordingly, most studies investigating the relationship between PA and Aβ deposition have been performed with transgenic mice overexpressing the *APP* gene, a model known to increase Aβ accumulation in the brain. Using such a model, Adlard et al provided mice with a running wheel for 1 and 5 months.[18] At the end of training, both groups exhibited a decreased number of Aβ deposits in the frontal cortex and hippocampus, along with improved spatial learning. These outcomes appear to have been mediated by alterations in APP processing. Similarly, forced treadmill training 5 days per week for 5 to 12 weeks was shown to significantly reduce Aβ deposition in the brain[19–21] and improve learning.[19] Conversely, Parachikova et al failed to detect alterations in Aβ and tau levels in models of AD involving middle-age and older mice and 3 weeks of free running[22]; it seems plausible that advanced neuropathology in the mice, in conjunction with the brevity of the study, contributed to these negative results (Tab. 1).

Consistent with the hypothesis that PA modulates Aβ turnover, the Australian Imaging, Biomarkers and Lifestyle Study of Ageing demonstrated that higher levels of self-reported PA were associated with a significant reduction in plasma Aβ deposition during aging in people who were healthy.[23] Moreover, a negative trend between PA levels and Aβ deposition in the brain was found, although this trend did not reach statistical significance.[23] In a study conducted in the United States, Liang et al[24] reported a negative correlation between PA (eg, self-reported voluntary walking, jogging, and running for a 10-year-period) and Aβ deposition. Interestingly, people who were middle-aged or older and met or exceeded the American Heart Association's guidelines (30 minutes of moderate exercise 5 days per week) showed a significantly lower level of Aβ than controls.[24] Together, this evidence suggests that PA decreases pathological Aβ deposition in the brain during normal aging and the early stages of AD.

Table 1.

Effects of Physical Activity on Cognitive Function and Alzheimer Disease (AD)–Related Neurobiological Features in Rodent Models of Alzheimer Disease[a]

Rodent Model	Targeted Gene[b]	Age (mo)	Modality	Frequency and Duration	Cognitive Assessment and Outcome	AD-Related Neurobiological Outcome	Study
ICV injection of Aβ	NA	2–4	Resistance exercise (swimming with tail weights)	5 d/wk × 8 wk	↑ Exploratory behavior (open field)	↓ Inflammatory markers	Souza et al,[85] 2013
SAMP8	NA	10	Running wheel	Free access × 24 wk	NA	↑ *BDNF* gene expression	Alvarez-Lopez et al,[117] 2013
APP695/PS1A246	*APP/PS1*	24	Treadmill	5 d/wk × 5 wk	↑ Spatial learning (MWM)	↓ Aβ deposition	Ke et al,[21] 2011
NSE/hTAU23	*TAU*	16	Treadmill	1 h/d × 5 d/wk × 12 wk	NA	↓ Inflammatory markers	Leem et al,[84] 2011
ICV injection of streptozotocin	NA	3	Treadmill	Daily × 5 d/wk × 5 wk	↑ Spatial learning (MWM)	↑ Antioxidant molecules; ↓ oxidative stress	Rodrigues et al,[118] 2010
APP23	*APP*	6 and 18	Running wheel	Free access × 10 d	NA	↓ Aβ deposition in 18-mo group; ↑ neurogenesis in 18-mo group	Mirochnic et al,[119] 2009
ICV injection of Aβ25-35	NA	2	Running wheel	Free access × 12 d	↑ Spatial learning (Y maze)	↑ Synaptogenesis	Wang et al,[120] 2013
APP/PS1	*APP/PS1*	3	Treadmill	30 min/d × 5 d/wk × 20 wk	NA	↓ Aβ deposition; ↓ Tau phosphorylation	Liu et al,[121] 2013
PS2 mutant	*PS2*	24	Treadmill	60 min/d × 5 d/wk × 12 wk	↑ Spatial learning (MWM)	↓ Aβ deposition; ↓ Aβ42; ↓ inflammatory markers	Kang et al,[20] 2013
ICV injection of Aβ1-42	NA	Adult (age not specified)	Treadmill	2 sessions/d (15 min each) × 2/wk progressing to 3 sessions/d × 5 d × 2 wk	↑ Spatial learning (RAWM)	↑ BDNF protein	Dao et al,[122] 2013
CRND8	*APP*	2.5	Running wheel	Free access × 10 wk	↔ Spatial learning (Barnes maze); ↓ stereotypic behavior (eg, jumping, climbing, and bar chewing)	↔ Aβ deposition; ↔ stress hormones	Richter et al,[123] 2008
Tg2576	*APP*	15–19	Running wheel	Free access × 3 wk	↑ Spatial learning (RAWM)	↔ Aβ deposition; ↑ levels of immune system–related protective molecules	Parachikova et al,[22] 2008
Damaged cholinergic neurons	NA	Age not specified	Treadmill	60 min/d × 7 d/wk × 8 wk	↑ Spatial learning (MWM)	NA	Hoveida et al,[124] 2011
Tg2576	*APP*	5	Running wheel	60 min/d × 5 d/wk × 12 wk	↔ Novel object discrimination	↓ Aβ plaques	Yuede et al,[125] 2009
3×AD	*APP, TAU, PS1*	1 and 9	Running wheel	1 mo old: free access × either 4 or 36 wk; 9 mo old: free access × 44 wk	↔ Spatial learning (MWM)	↔ BDNF; ↔ Aβ; ↔ pTau	Marlatt et al,[52] 2013

(Continued)

Table 1.
Continued

Rodent Model	Targeted Gene	Age (mo)	Modality	Frequency and Duration	Cognitive Assessment and Outcome	AD-Related Neurobiological Outcome	Study
3×Tg-AD	*APP,PS1, TAU*	1, 3, and 6	Running wheel	Free access × 4 and 24 wk	↑ Spatial learning (MWM)	↔ pTau; ↓ Aβ42	Garcia-Mesa et al,[38] 2011
3×Tg-AD	*APP,PS1, TAU*	1	Running wheel	Free access × 24 wk	NA	↑ Synaptic proteins; ↓ GABA A receptor 5 subunit; ↑ NMDA receptors	Revilla et al,[126] 2014
APOE ε4	*APOE*	10 and 12	Running wheel	Free access × 6 wk	↑ Spatial learning (MWM)	↑ Synaptic function; ↑ BDNF; ↔ pTau; ↔ amyloid	Nichol et al,[39] 2009
Tg2576	*APP*	16–18	Running wheel	Free access × 3 wk	NA	↑ BDNF; ↔ Aβ; ↓ inflammatory markers	Nichol et al,[81] 2007
Tg2576	*APP*	15–19	Running wheel	Free access × 3 wk	↑ Spatial learning (MWM)	↔ Aβ; ↔ pTau	Parachikova et al,[22] 2008
Tg2576	*APP*	16–18	Running wheel	Free access × 3 wk	↑ Spatial learning (RAWM)	↓ Inflammatory molecules; ↓ activated microglia; ↓ Aβ levels	Nichol et al,[39] 2009 Nichol et al,[81] 2007
TgCRND8	*APP*	1 and 1.5	Running wheel	Free access × 4 and 20 wk	↑ Spatial learning (MWM)	↓ Aβ42 deposition	Alard et al,[18] 2005
Thy-Tau22	*TAU*	3–12	Running wheel	Free access × 36 wk	↑ Spatial learning (Y maze)	↑ BDNF; ↓ pTau	Belarbi et al,[33] 2011
3×Tg-AD	*APP,PS1, TAU*	6	Treadmill	15–30 min/d × 7 d/wk × 5 wk	↔ Spatial learning (MWM)	↔ pTau; ↓ Aβ42	Giménez-Llort et al,[127] 2010
Aβ25-35	NA	1.75	Treadmill	30 min/d × 5 d/wk × 4 wk	↑ Short-term memory (step-through avoidance task)	↑ Neurogenesis; ↑ BDNF	Kim et al,[53] 2014
NSE/APPsw	*APP*	12 and 13	Treadmill	60 min/d × 5 d/wk × 16 wk	↑ Spatial learning (MWM)	↓ Aβ42	Um et al,[128] 2008
Tg-NSE/hTau23	*TAU*	16	Treadmill	60 min/d × 5 d/wk × 12 wk	NA	↓ pTau	Leem et al,[32] 2009
Tg-NSE/PS2m	*PS2*	24	Treadmill	60 min/d × 5 d/wk × 12 wk	↑ Spatial learning (MWM)	↓ Aβ42 deposition; ↓ pTau	Um et al,[19] 2011

[a] Accepted scientific nomenclature establishes that all letters should be uppercase for human gene or protein designations (eg, APP), whereas only the first letter should be uppercase for rodent gene or protein designations (App). Moreover, gene designations should be italicized (*APP*), but protein designations should not (APP). The Morris water maze (MWM), Y maze, radial arm water maze (RAWM), and Barnes maze were used for spatial learning assessments in rodents. ICV=intracerebroventricular, Aβ=amyloid beta, NA=not assessed, ↑=increase, ↓=decrease, BDNF=brain-derived neurotrophic factor, APP=amyloid precursor protein, PS1=presenilin 1, PS2=presenilin 2, ↔=no change, pTau=phosphorylated tau, GABA=γ-aminobutyric acid, NMDA=*N*-methyl-D-aspartate.
[b] These mice overexpress human genes.

Table 2.

Effects of Physical Activity on Cognitive Outcomes in People With Alzheimer Disease (AD)[a]

AD Intervention	Sample (n)	Dementia Severity as Determined by MMSE	Age (y)	Sex	Modality	Frequency and Duration	Assessment	Study
Randomized control	14	14.3	76.8	5 men, 9 women	Walking, strengthening, flexibility, balance training, agility	1-h session × 3 sessions/wk × 24 wk	↓ Severity of sleep disturbances	Nascimento et al,[98] 2014
Randomized control	32	<23	81.8	4 men, 12 women	Walking	1-h session × 3 sessions/wk × 15 wk	Positive correlation with ERFC	Kemoun et al,[101] 2010
Randomized control	27	≥10	74–76.5	8 men, 19 women	Walking	Single session daily × 12 wk	↔ MMSE	Steinberg et al,[105] 2009
Randomized control	21	5–15	84.0	30 men, 5 women	Walking	30-min session × 4 sessions/wk × 24 wk	↓ Rate of decline in MMSE	Venturelli et al,[106] 2011
Randomized control	40	10–28	51–89	16 men, 24 women	Walking, strengthening, balance training	1-h session/wk × 6 wk	↑ MMSE; ↑ ADAS-cog	Vreugdenhil et al[102] 2012
Randomized control	27	12–29	72.0	11 men, 16 women	Brain Gym Exercise Protocol	1-h session/wk × 6 wk	↑ Cantab-Expedio	Yaquez et al,[103] 2011
Nonrandomized control	30	19.4	77.0	6 men, 24 women	Aerobic training, strengthening, flexibility, balance training	1-h session × 5 sessions/wk × 16 wk	↑ MCE	de Andrade et al,[104] 2013
Randomized control	27	19	77.5	Not reported	Aerobic training, strengthening, flexibility, balance training, agility, cognitive activities	1-h session × 3 sessions/wk × 16 wk	↑ Executive functions, including FAB	Coelho et al,[72] 2013
Randomized control	21	Not applicable	76.0	Not reported	Treadmill	1 session starting at 4 km/h with slope of 3% and increasing slope by 1% every 3 min until heart rate reached 85% of maximum capacity	↑ Plasma BDNF in controls and cases with AD	Coelho et al,[129] 2014

[a] Among the cognitive assessments used in these studies were Cantab-Expedio, which measures sustained attention and visual memory; the Montreal Cognitive Assessment (MCE), which assesses frontal cognitive function, attention, and language; and the Mini-Mental State Examination (MMSE), which is an objective measure of cognitive function that examines several parameters (including orientation with regard to time and place, registration [eg, repeating prompts], attention and calculation [eg, backward spelling task], recall, language, and repetition [eg, verbalizing names of objects and complex commands]). Mini-Mental State Examination scores ranging from 0 to 9 indicate severe cognitive impairment, those ranging from 10 to 18 indicate moderate impairment, and those ranging from 19 to 24 suggest mild cognitive impairment. The Brain Gym Exercise Protocol consists of fine motor, balance, and eye-hand coordination activities. ERFC=Rapid Evaluation of Cognitive Functions Test, ADAS-cog=Alzheimer's Disease Assessment Scale–cognitive subscale, FAB=Frontal Assessment Battery, BDNF=brain-derived neurotrophic factor.

Evidence That PA Alters Tau Accumulation

Microtubules are structures that facilitate the transport of a variety of molecules (eg, nutrients and growth factors) bidirectionally between the cell body and axon terminals in neurons. Typically, tau proteins bind to microtubules and stabilize them. However, chemical alterations of tau by various kinases and phosphatases produce a form of tau with altered biological function and interrupt its binding to microtubules.[25] Consequently, tau proteins disengage from microtubules and clump together with other tau threads. Lacking appropriate stabilization, the microtubules disassemble and become enmeshed with the tau threads, forming NFTs.[26] The collapse of microtubules and tau assembly results in significant alterations in internal transport and, consequently, atrophy and dysfunction of neurons.

Indeed, the pattern of axonal transport collapse, NFT formation, and neurodegeneration is well characterized in AD. Neurofibrillary tangles appear first in the transentorhinal region and later in the hippocampal formation before spreading outward to the rest of the brain[27] (Fig. 1). Given that a 4- to 8-fold increase in tau phosphorylation has been reported in postmortem brain samples from people with AD[28] and that tau pathology interrupts the vital process of intracellular neuronal transport,[29] it is generally held that tau pathology plays an important role in inducing neurodegeneration in AD.[30]

Interestingly, evidence has suggested that PA reduces the level of tau deposition by modifying the activity of tau-related kinases and phosphatases.[31,32] Leem et al[32] demonstrated that mice overexpressing the gene for abnormal tau showed a significant increase in glycogen synthase kinase 3β levels. This enzyme is believed to play a vital role in tau phosphorylation and accumulation. Notably, treadmill training for 12 weeks led to a significant reduction in glycogen synthase kinase 3β levels, suggesting that exercise can reduce tau phosphorylation.[32] In another model of AD, Um et al[19] demonstrated that 3 months of treadmill training of extremely old mice led to a significant reduction in tau phosphorylation in the hippocampus. In yet another model, Belarbi et al[33] demonstrated that 9 months of free access to a running wheel decreased the early stages of NFT formation in the hippocampal region and improved spatial learning. Together, the results of these preclinical studies suggest that PA might provide a means to alleviate tau pathology and improve cognitive function in AD.

Evidence That PA Alters Synaptic Function and Number of Synapses

As fundamental sites of communication between neurons, synapses play an important role in cognition. Alterations in synapses adversely affect cognitive function by altering local and regional communication, which is essential for proper brain function. Indeed, the loss of synapses is an invariant and early characteristic of AD, and there is a strong relationship between the degree of synaptic loss and the severity of cognitive decline.[34–36]

Quantification of synaptic markers in postmortem samples from people with AD has revealed a reduction in the number of synapses in areas of the brain vitally important for learning and memory, particularly the association cortices and hippocampal region.[35,36] Altered expression of synaptic proteins occurs early during the progression of AD,[36] with concomitant disruption in neuronal communication. As AD progresses, neurons increasingly shrink and lose more and more synaptic connections. By the final stages of the disease, significant neuronal loss and brain atrophy have occurred to the point at which the ability to acquire and encode new memories has been lost.[37]

Transgenic mouse models of AD have shown similar alterations in synaptic function, along with concomitant deficits in spatial learning and memory.[38,39] However, chronic PA in the form of free access to a running wheel for 4,[38] 6,[39] and 24[38] weeks has been shown to significantly improve the synaptic properties of the hippocampus and spatial learning (Tab. 1). The lack of noninvasive methods for the study of synaptic function precludes direct examination in humans, prompting the use of proxy measures. For instance, Pajonk et al showed that people who were healthy and regularly participated in PA (eg, aerobic exercise 3 times per week, 30 minutes per session, for 12 weeks) demonstrated improved hippocampal volume, as studied by magnetic resonance imaging[40]; this finding could be attributed to increased neuronal numbers, their projections, number of synapses, or a combination of these. Together, the results of these studies make it seem plausible that PA might promote synaptic function and cognitive function in AD, particularly in the hippocampus.[41]

Evidence That PA Restores Neurogenesis

In mammals, an estimated 700 neurons are produced daily in a process called neurogenesis.[42] This process occurs in 2 regions of the adult brain: the subventricular zone and the subgranular zone of the hippocampus.[43,44] Many of the 20,000,000 neurons generated over the course of a lifetime migrate to the dentate gyrus of the hippocampus and

become integrated into circuits that play a vital role in learning and memory.[45,46] However, several intrinsic factors (eg, growth factors, cytokines, hormones) and extrinsic factors (eg, PA, pharmacological agents, hippocampus-dependent learning tasks) can alter the rate of neurogenesis.[47] Such is the case in aging and AD, in which several known and unknown factors compromise neurogenesis.[45,48]

Notably, rodent studies have suggested that PA can potently induce neurogenesis in the dentate gyrus of the hippocampus, a brain structure that is vitally important for learning and memory[49,50] and yet is vulnerable in AD.[51] This knowledge has led to the suggestion that PA might be deployed to mitigate AD-related decrements in neurogenesis. Indeed, Marlatt et al[52] demonstrated that both short-term (1 month) and long-term (9 months) free access to a running wheel led to a significant increase in neurogenesis in the hippocampus in a mouse model of AD (eg, 3xAD, mice overexpressing *APP*, *TAU*, and *PS1*). Using another rodent model of AD, Kim et al[53] injected Aβ—a protein that accumulates in plaques in the brain—into the brain ventricles of rats, inducing significant cognitive dysfunction and a reduction in neurogenesis. Next, they exposed the rats to treadmill training (30 minutes per day, 5 days per week, for 4 weeks), partially restoring hippocampal neurogenesis[53] (Tab. 1). An improvement in the rate of neurogenesis is an important target in AD because enhanced neurogenesis in animal models has been positively correlated with improvements in learning and memory,[45,54-56] and the blockade of neurogenesis after PA has been shown to negate improvements in memory and learning.[57]

Further attesting to the importance of neurogenesis in memory and learning is a recent clinical study demonstrating a positive association between neurogenesis and declarative memory function in humans.[58] Thus, the idea that hippocampal neurogenesis can be positively affected by PA offers considerable hope for exploiting newly born cells to reestablish hippocampal brain circuits that have been damaged as a result of the progression of AD.

Evidence That PA Increases Neurotrophin Levels

Neurotrophins—vital proteins in the brain—are known to contribute to the survival, growth, and maintenance of neurons, enabling them to participate in a variety of specific functions, including learning and memory.[11] Failure in neurotrophin release, binding, and action plays a significant role in neurodegenerative disorders, particularly AD.[59] Indeed, it has been shown that brain-derived neurotrophic factor (BDNF)—one of the most widely distributed neurotrophins in the brain—plays a vital role in the maintenance of neurons that underlie cognition, including those that undergo degeneration in AD.[60,61] Moreover, a host of BDNF-related abnormalities have been reported in AD. It has been shown that levels of BDNF in serum decrease during the course of AD and that the decrease correlates well with the severity of dementia[62]; postmortem brain samples from people with AD exhibit reduced BDNF gene expression[63,64]; a common variation in the BDNF gene is associated with late-stage AD[65]; the gene encoding BDNF is associated with AD-related depression[66]; there is an inverse relationship between the presence of NFTs and BDNF levels[67]; and BDNF levels in mouse models of AD correlate well with the severity of AD neuropathology.[68]

Because of the responsiveness of BDNF to PA, multiple laboratories have focused on BDNF in recent years.[69,70] It has been shown that mouse models of AD that express the human apolipoprotein $\epsilon 4$ allele exhibit increased levels of hippocampal BDNF and its TrkB receptors after 6 weeks of voluntary wheel running.[39] Such a finding is important because the apolipoprotein E $\epsilon 4$ allele has been shown to be a major risk factor for AD[71] and because increased levels of BDNF might preserve neuronal function in models affected by this genetic background. Using another transgenic mouse model of AD, Belarbi et al[33] demonstrated that 9 months of voluntary free wheel running significantly increased BDNF levels in the brain. Notably, other investigators have shown that voluntary running is associated with rapid increases in BDNF gene expression in the hippocampus and that these changes endure for weeks.[41] Paralleling these findings, in people who were healthy and people who had AD, acute aerobic PA (until the heart rate reached 85% of the maximum capacity) was shown to increase plasma BDNF levels,[72] a significant finding given that plasma BDNF levels are linked to alterations in brain BDNF levels.[73]

Given that PA alters levels of BDNF and that normalized neurotrophin levels are often associated with concomitant improvements in cognition, it seems plausible that PA could be deployed to mitigate cognitive dysfunction in AD[2,59,74] without necessarily reversing extant neuropathology.

Evidence That PA Positively Alters Inflammation and Immune Function

Inflammation is a complex cellular and molecular defense mechanism designed to protect against stress, infection, and injury.[75] In the brain, this process is characterized by the activation of inflammatory cells (eg, astrocytes and microglia) and the

release of inflammatory molecules, such as interleukin 1β, interleukin 6, and tumor necrosis factor α.[76] Secreted inflammatory molecules recruit other immune cells, such as monocytes and lymphocytes, to cross the blood-brain barrier and induce neuroinflammation in the brain.[77] Several studies have implicated overactive neuroinflammatory processes in AD. For example, it has been shown that there are elevated levels of inflammatory molecules in regions adjacent to Aβ plaques[78] as well as in cerebrospinal fluid,[79] altered lymphocyte and macrophage distributions in the brain,[80] and increased activation of inflammatory cells (including astrocytes and microglia)[41]; in addition, a reduced risk of dementia has been reported in people receiving anti-inflammatory drugs. Whether the relationship of the immune response to AD is primary or secondary has yet to be determined; nevertheless, the suggestion that PA might play an anti-inflammatory role in AD by mitigating neuronal dysfunction, the occurrence of Aβ pathology, and neurodegeneration warrants close consideration.

Animal and human studies have shown that PA reduces markers of neuroinflammation in AD.[39,81] Nichol and colleagues[39,81] demonstrated that transgenic mice overexpressing *APP* showed increased levels of inflammatory markers (eg, interleukin 1β and tumor necrosis factor α) in the brain but that 3 weeks of free wheel running reduced the levels of these inflammatory markers to normal; these findings coincide with improvements in spatial learning. This evidence makes it seem plausible that PA induces the release of anti-inflammatory (interleukin 6)[82,83] and adaptive (CXCL1 and CXCL12) immune molecules from the muscle and brain,[22] mitigating an exaggerated inflammatory response.[82–85] Bolstering these findings are the results of epidemiological studies demonstrating that habitual PA is correlated with reduced systemic inflammation.[86] Moreover, a randomized controlled trial (RCT) in aging adults who were healthy and participated in progressive aerobic activity (15 minutes increasing to 40 minutes) 2 times per week for 6 months revealed significant improvements in immune system function.[87] Similar results were found in a study of elderly women participating in aerobic exercise (60 minutes per session, 3 times per week, for 16 weeks).[88]

Notably, several human studies have failed to replicate the positive effects of PA on immune function in young and elderly people, possibly reflecting influences that have not been taken into account. Nevertheless, current exercise guidelines issued by the American College of Sports Medicine and the Surgeon General suggest that moderate exercise (5–60 minutes at 40%–60% of aerobic capacity) can be used to induce positive immune health.[89] This notion is reaffirmed by a consensus statement drafted by international experts in the field of exercise immunology; this statement suggests that moderate levels of regular exercise might be particularly beneficial in elderly people,[86] a population at high risk for AD. Together, this evidence suggests that moderate levels of PA might modulate AD pathology by decreasing systemic inflammation and altering immune function.

Evidence That PA Affects Circadian Rhythms

Many physiological processes, such as feeding behavior, motor activity, hormonal secretion, and autonomic nervous system functions, exhibit naturally occurring rhythms that are commonly referred to as circadian rhythmicity.[90] Central to circadian rhythmicity is the suprachiasmatic nucleus (SCN), a structure located in the anterior hypothalamus and comprising neurons that regulate different body functions according to rhythms that vary with the 24-hour night-day light cycle. More specifically, the SCN receives direct inputs from the retina, and these cues regulate its pattern of activity. Other major sources of input to the SCN include brain-stem nuclei and the somatosensory cortex.

Disturbances in SCN function have been linked to neuropathological changes. It has been shown that complete bilateral destruction of the SCN leads to a day-night reversal in wake-sleep rhythmicity.[91] Moreover, sleep alterations have been associated with SCN abnormalities in several neurodegenerative disorders, including AD.[91] The SCN exhibits a higher level of neuropathology in people with AD than in controls, resulting in a significant loss of SCN neurons and sleep fragmentation symptoms. Indeed, 25% to 40% of people with mild to moderate AD exhibit significant sleep problems, including a decrease in amplitude in circadian rhythms and a phase delay.[92] These changes in sleep patterns seem to precede cognitive symptoms in people with AD, with decrements in sleep quality paralleling both cognitive dysfunction and the progression of AD pathology.[92]

Given that both intrinsic and extrinsic factors are capable of regulating SCN activity, it seems plausible that modifiable factors such as PA,[93] light exposure,[94] and pharmacotherapeutics (eg, melatonin)[95] could be used to assuage rhythmic abnormalities and sleep fragmentation in AD. It appears that PA can modulate SCN activity by either regulating body temperature or altering the activity of several brain regions that project to the SCN (eg, raphe nucleus, pineal gland).[91] Consequently, PA has been used to qualitatively and quantita-

tively improve atypical sleep symptoms across patient populations.[96]

In a recent cross-sectional study examining levels of PA in people diagnosed with lung cancer, a significant positive correlation was noted between self-reported levels of PA—which included light activities (eg, cooking, slow walking, driving, and performing light manual work), moderate activities (eg, playing golf, cycling less than 9.6 km [6 miles] per hour, walking 3.2–4.8 km [2–3 miles] per hour, loading and unloading goods), and vigorous activities (eg, swimming, jogging, hiking, gymnastics, and dancing)—and overall sleep time and quality.[96] Similarly, in another cross-sectional study, Hooghiemstra et al noted that people with early-onset dementia exhibited disturbances in rest-activity rhythm variables.[97] More importantly, they noted a significant negative correlation between PA, as measured by the number of daily steps taken, and the severity of rest-activity rhythm disturbances; this finding led them to advocate for increased ambulatory activities for people with dementia. However, to our knowledge, only one interventional study has examined the effects of PA on sleep quantity and quality in AD.[98] Nascimento et al[98] reported that 6 months of PA (eg, walking, circuit training, stretching, balance, agility) decreased the frequency of sleep disturbances in people with mild to moderate AD.

Given that circadian rhythm abnormalities and sleep fragmentation are the most common causes of institutionalization for people with AD, more research is needed to understand how PA improves circadian rhythms and, in turn, cognitive function.[99] Thus, although the practical implications of these findings remain to be clarified, they suggest that the treatment of sleep abnormalities is an emerging approach for mitigating AD-related symptoms.[100]

Evidence That PA Improves Cognition in People With AD

Current research on AD has demonstrated the feasibility of implementing PA to improve cognitive function (Tab. 2). Most RCTs have reported positive associations between PA and cognitive function.[72,101–104] Most of the PA training ranges in the extant RCTs were designed to facilitate active participation for 2 to 3 hours per week for a duration of 3 months or longer,[72,101,104–106] although 2 programs had a 6-week duration.[102,103] The modalities used in the programs varied, with all programs having some form of locomotor activity as a core component,[72,101,102,104–106] except one.[103] Three programs included locomotion in addition to balance and strength training.[72,102,104] For most of the programs,[72,101–104] a positive association between PA and cognitive function was noted. More specifically, a positive correlation between cognitive status and PA was noted for most of the programs,[72,101–104] but a decrease in the rate of cognitive decline was noted for one program.[106] The one program failing to show positive effects of PA on cognition was implemented by caregivers in the home environment.[105] Of particular note in the latter study were depressive scores that were significantly higher in the group of people participating in PA than in people in the control group,[105] suggesting that depressive symptoms might have limited the positive effects of PA on cognition in that study.

Extensive variations existed in the studies reviewed with regard to age, sex, the presence of movement-limiting factors, diagnosis (AD plus vascular dementia versus pure AD), and cognitive tests, yet all reported positive results. Nevertheless, these extant RCTs are few and leave many questions unresolved. These studies need to be replicated as larger RCTs while disentangling the effects of genetically homogeneous groups (eg, matching for apolipoprotein E genotype), duration (6 weeks, 12 months, and 24 weeks), and disease stage. Moreover, studies in which PA and cognitive changes are combined with biomarker analysis (eg, Aβ and tau levels in cerebrospinal fluid and plasma and in vivo imaging for assessment of brain structural alterations as well as Aβ and tau accumulation) and cognitive assessment are needed.

Implications for Physical Therapists, Unresolved Issues, and Future Directions

Finding an effective treatment for AD-related cognitive decline is an unmet goal. However, considerable progress has been made in better understanding implicated features and processes. Here we presented biomedical evidence that supports the role of PA in optimizing multiple mechanistic pathways believed to underlie the disease process involved in cognitive decline in AD. The data suggested that PA might be used as a preventive therapeutic approach for people who are healthy or asymptomatic and for treating people with evidence of clinical cognitive impairment so as to delay the onset of full-blown symptoms. Earlier application of PA to mitigate pathological processes and to assuage cognitive decline is imperative given recent evidence from clinical trials suggesting that interventions applied earlier in the course of AD are more likely to achieve disease modification, whereas those applied later have a significant but more limited effect after the emergence of neuronal degeneration.[107] However,

the success of prevention campaigns will require significant changes in philosophy and approach. PA must be advocated as a preventive therapeutic approach, with the goal of reducing neuropathology by promoting the initiation of good health habits that delay progression and overt cognitive decline. This preventive approach must be paralleled with research efforts aimed at revealing the effects of PA at different points in the disease continuum.

There is clearly an urgent need to identify the optimum mode, intensity, and duration of PA that might alter AD-related pathology. Several studies have suggested that exercise interventions combining various modalities, such as aerobic and strength training activities, are more effective in enhancing cognitive health in humans than interventions emphasizing aerobic activities alone. For instance, a meta-analysis by Colcombe and Kramer revealed that people who participated in a combination of aerobic and strength training activities showed greater gains in cognition than those who participated in aerobic activities alone (effect sizes of 0.59 versus 0.41, $n=101$, $P<.05$).[108] Similarly, a meta-analysis by Smith et al revealed that interventions consisting of aerobic and strength training activities improved attention, processing speed, and working memory to a greater extent than aerobic exercises alone in both people who were healthy and those with mild cognitive impairment (MCI)[109]; this effect likely was mediated by alterations in hippocampal volume.[110,111]

Hippocampal atrophy has been linked to increased risk of progression from MCI to AD, and the reversal of cognitive status from MCI to normal cognition has been linked to greater hippocampal volume.[112,113] Notably, 1 year of aerobic exercise of moderate intensity was shown to improve memory and hippocampal volume in older adults who were healthy, effectively reversing age-related loss of volume by 1 to 2 years.[110] Directly applying these data, Makizako et al[111] demonstrated that hippocampal volume was the link between moderate PA and memory augmentation in people with MCI and that longer durations of moderate PA could result in increased hippocampal volume and improved memory.

Together, these findings suggest that PA elicits compensatory mechanisms in the brains of people with extant neuropathology and, in turn, improves cognitive function. Nevertheless, the dosages (frequency, intensity, and duration) that effectively elicit neuroprotective effects have not been fully determined. One study showed that people who were middle-aged, healthy, and exercised 2 times per week for 20 to 30 minutes reduced the risk for AD by half.[114] However, it seems likely that people with cognitive impairments will require higher dosages of PA to positively affect cognitive function. According to Heyn et al,[115] moderate exercise (36–45 minutes per session, 3 or 4 times per week, for 14.5–23.4 weeks) had a strong positive effect on cognition in elderly people with cognitive dysfunction ranging from MCI to dementia. Similarly, Lautenschlager et al[116] showed that 150 minutes of moderate exercise (50 minutes per session, 3 times per week, for 24 weeks) had a positive effect on cognitive function in people with MCI.

In contrast to earlier studies relating different aspects of cognitive function to PA without considering underlying brain changes, we investigated how PA alters key features of AD pathology and, in turn, might be used to improve cognitive function. In summary, the data presented here suggest that moderate PA—a target that is practical, well tolerated, and likely to optimize exercise adherence—can be used to improve cognitive function and reduce the slope of cognitive decline in people with dementia of the AD type. It is imperative that physical therapists stay informed about new developments in the field of exercise neuroscience to function as independent and skilled practitioners.

Dr Phillips and Dr Salehi developed the concept for the study. Dr Phillips, Dr Akif Baktir, and Dr Salehi provided writing. Dr Phillips, Dr Das, Mr Lin, and Dr Salehi provided data collection. The authors thank Ms Persia Salehi for professional graphic work in preparing Figure 1.

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