EXTRA Dementia and Geriatric Cognitive Disorders

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Review Article

Exercise and Early-Onset Alzheimer's Disease: Theoretical Considerations

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Key Words
Dementia · Early-onset Alzheimer's disease · Early-onset dementia · Intervention · Physical activity · Presenile dementia

Abstract
Background/Aims: Although studies show a negative relationship between physical activity and the risk for cognitive impairment and late-onset Alzheimer's disease, studies concerning early-onset Alzheimer's disease (EOAD) are lacking. This review aims to justify the value of exercise interventions in EOAD by providing theoretical considerations that include neurobiological processes. ***Methods:*** A literature search on key words related to early-onset dementia, exercise, imaging, neurobiological mechanisms, and cognitive reserve was performed. ***Results/Conclusion:*** Brain regions and neurobiological processes contributing to the positive effects of exercise are affected in EOAD and, thus, provide theoretical support for exercise interventions in EOAD. Finally, we present the design of a randomized controlled trial currently being conducted in early-onset dementia patients.

Introduction

Epidemiological studies demonstrate a positive relationship between physical activity and cognitive functioning [1, 2]. A decrease in the level of physical activity by a disturbance in gait and, consequently, in walking coincides with a decline in cognitive functioning [1]. A

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decrease in the level of physical activity might even predict dementia [3]. In contrast, maintaining a physically active lifestyle may protect against dementia [4, 5].

A causal relationship, i.e. does physical activity improve cognitive functioning, can only be demonstrated by randomized controlled trials (RCTs). In one study, a daily physical activity intervention in healthy sedentary older persons improved executive functions, in particular working memory [6]. Intervention studies that examine the effects of physical activity on cognition in demented patients are limited and show mixed results. Positive effects on executive functions after aerobic exercise were found in small groups of elderly patients suffering from mild cognitive impairment [7]. Another study also observed positive effects of exercise on cognitive functioning in older persons at risk for Alzheimer's disease (AD) [8]. In contrast, in older persons with moderate dementia, no positive effects on cognition were found, potentially explained by the fact that most of the patients were suffering from concomitant cardiovascular disease [9] (for a review, see [10]). In summary, positive effects of physical activity have been found in healthy older individuals, patients with mild cognitive impairment, and persons at risk for AD. In persons with moderate dementia, these positive effects were not found.

One of the brain regions that play a crucial role in executive functions is the prefrontal cortex [11]. The functions of the prefrontal cortex react positively to increased physical activity [12]. The functioning of other cortical areas, such as the parietal lobe, also show a positive relationship with physical activity [13]. The prefrontal and parietal lobes are particularly vulnerable in early-onset Alzheimer's disease (EOAD) [14, 15]. It is therefore remarkable that studies examining the effects of physical activity in this population are lacking.

Studies on the effects of physical activity interventions on cognition in this younger population may be worthwhile for a number of reasons. Firstly, few specific treatments are available for patients with EOAD. However, EOAD is increasingly recognised as a problem [16]. It places a large psychological and economic burden on patients and caregivers because of the patient's prominent role in society at the time of disease onset [17]. A treatment, such as a physical activity program, might bring positive effects for both the patient and the caregiver. Secondly, EOAD patients suffer less from physical inconveniences [18] and may therefore participate in a more intensive program; intensity of an exercise program is important for its effect on cognition [19]. Finally, positive effects of exercise on cognition in normal ageing and (very) early dementia can be explained by their beneficial impact on several neurobiological processes, such as neurogenesis, synaptogenesis, and angiogenesis [20]. Improvement of these processes may also benefit patients with EOAD.

The goal of the present review is to provide theoretical considerations that justify exercise interventions in EOAD. Within this scope, we will address the following topics. First, the physical functioning of EOAD patients will be addressed. Subsequently, brain regions that respond positively to exercise and that are affected in EOAD will be discussed. Next, neurobiological mechanisms such as neurogenesis, synaptogenesis, angiogenesis, and neurotrophins that may underlie the effects of exercise on cognition in EOAD will be highlighted. Subsequently, the cognitive reserve hypothesis will be reviewed. Finally, we present the design of an RCT currently being conducted in early-onset dementia (EOD) patients in our centre.

Methods

Search databases were PubMed/MEDLINE and Web of Science. The search terms used were combinations of the key words early-onset and presenile in combination with dementia, Alzheimer's disease, vascular dementia, and frontotemporal dementia. During the literature

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search, it appeared that studies on EOD involve almost exclusively studies on EOAD. Therefore, this review targets exclusively this type of EOD.

With respect to studies on physical functioning, the following search terms were used: physical functioning, gait (disturbance*), balance, falling, and walking (speed). The search for imaging studies included the following search terms: image*, damage*, atrophy*, degenerate*, single-photon emission computed tomography (SPECT), (functional) magnetic resonance imaging ((f)MRI), and positron emission tomography (PET), in combination with the terms brain, cortical, cerebral, lobe, cerebrum, encephalon, and grey matter. In relation to exercise, only studies concerning structural MRI were included. Studies on neurogenesis were searched using the terms neuro*, brain, cell, and dendri*, in combination with genesis, growth, branch*, survival, prolifera*, plastic*, death, damage, atrophy*, and degenerat*. The search for studies on synaptogenesis included the term synap*, in combination with genesis, formation, elimination, pruning, synaptophysin, and synaptotagmin. With respect to studies focusing on angiogenesis, the following search terms were used: angio*, arterio*, vessel*, and vascul*, in combination with genesis, growth, branch*, prolifera*, death, deterioration, elimination, and SPECT. Neurotrophin studies were gathered by the search terms neurotrophin*, neurotrophic factor, brain-derived neurotrophic factor (BDNF), neurotrophin-4 (NT-4), nerve growth factor (NGF), neurotrophin-3 (NT-3), insulin-like growth factor (IGF), and new-neurotrophin-1 (NNT-1). Studies regarding the cognitive reserve hypothesis included the search terms cognitive reserve, brain reserve, and neural reserve. Studies were first selected based on the title. Subsequently, the residual studies were selected using the abstract and the content of the article. The final search was performed in June 2011.

Physical Functioning of EOAD Patients Compared to Late-Onset Alzheimer's Disease Patients

We found one study on gait disturbances in EOAD compared to late-onset Alzheimer's disease (LOAD) showing that EOAD patients experience less gait disturbances (16% of the patients) than LOAD patients (45%) [18]. In LOAD, gait disturbances have recently been studied (for reviews, see [21–23]). Gait disturbances are caused by neuropathology in subcortical brain regions, e.g. basal ganglia, and in cortical areas, e.g. frontal lobe, and can hence be divided in parkinsonian and pseudoparkinsonian gait disturbances, respectively [24]. Gait disturbances can be experienced even in mild stages of AD (i.e. cautious gait) [25, 26] and include decreased gait velocity, step length, static and dynamic balance, and a widened base [27]. In more advanced stages of AD, a 'frontal gait' can be observed: patients show a shuffling walking style and start and turn difficulties [25].

Taken together, although studies are scarce, we assume that the physical condition of EOAD patients would permit participation in a more intensive exercise program than LOAD patients.

Brain Regions That Respond Positively to Exercise and Are Affected in EOAD

In individuals with higher levels of cardiorespiratory fitness, the loss of grey matter, characteristic for ageing, is reduced in prefrontal, superior and anterior parietal, medial temporal (specifically in the hippocampus), and occipital regions [12, 28–31]. It is known that exercise has a beneficial influence on cardiorespiratory fitness [32]. Indeed, after aerobic exercise, increases in grey matter density were observed in prefrontal and temporal cortices;

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Table 1. Brain regions that respond positively to exercise (structural MRI)

Reference	Design	Population (n)	Age, years[a]	Exercise measurement	Brain region
Colcombe et al. [12], 2003	Relational	Healthy older adults (55)	66.5 (5.3)	$VO_{2\ max}$ estimate	PFC, superior parietal
Colcombe et al. [33], 2006	RCT 6 months (aerobic training vs. stretching toning)	Healthy older adults (59), MRI of young controls (20)	EG 65.5 CG 66.9	$VO_{2\ max}$ estimate	PFC, temporal cortex
Erickson et al. [34], 2011	RCT 1 year (aerobic exercise vs. stretching)	Healthy older adults (120)	EG 67.6 (5.81) CG 65.5 (5.44)	$VO_{2\ max}$	Hippocampus
Erickson et al. [29], 2010	Relational	Healthy older adults (299)	78	Number of blocks walked in 1 week	PFC, occipital, entorhinal, hippocampus
Erickson et al. [28], 2009	Relational	Healthy older adults (165)	66.5 (5.6)	$VO_{2\ peak}$	Hippocampus
Gordon et al. [30], 2008	Relational	Healthy older adults (40), MRI of young controls (20)	71.5 (4.7)	$VO_{2\ max}$	Medial temporal, anterior parietal, inferior frontal
Rovio et al. [31], 2010	Follow-up (20.9 (4.9) years)[a] after survey	Healthy adults (31), MCI (23), dementia (21)	Active (n=32): 73.0 (3.5); sedentary (n=43): 72.1 (4.4)	At follow-up: indication of weekly participation in physical activity	Frontal

MCI = Mild cognitive impairment; EG = exercise group; CG = control group; $VO_{2\ max}$ = maximum oxygen volume; $VO_{2\ peak}$ = peak oxygen volume; PFC = prefrontal cortex.
[a] Mean with standard deviation in parentheses, unless otherwise specified.

concerning the latter, these increases are particularly seen in the hippocampus [33, 34]. For more details see table 1.

Neocortical atrophy is a neuropathological hallmark of EOAD [35–37]. MRI, SPECT, and PET imaging techniques show that the above-mentioned brain regions which respond positively to exercise are affected in EOAD [14, 15, 35, 36, 38–42]. For more details on the aforementioned areas and on areas affected in EOAD but not related to exercise, see table 2.

Of note is that the primary sensory and motor areas are relatively preserved in EOAD [35], implying that motor activity is still possible in these patients.

Neurobiological Mechanisms, Exercise, Cognition, and EOAD

Animal and human experimental studies show that 3 major neurobiological mechanisms underlie the positive effects of exercise on brain structures and subsequently on cognitive function: neurogenesis, synaptogenesis, and angiogenesis [20, 43, 44].

Neurogenesis

Exercise

In a landmark paper, cell proliferation and neurogenesis have been shown in the hippocampal area of mice having access to a running wheel [45]. Other studies report similar findings, suggesting that prolonged physical activity (voluntary wheel running) enhances neurogenesis in the hippocampus, both in adult mice and rats [46–48] as well as in aged mice and rats [49]. More specifically, wheel running in mice stimulates survival of newly generated neurons and their development into functional hippocampal neurons [50]. Further-

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Table 2. Brain regions that are affected in EOAD

Reference	Design	Population (n)	Age, years[a]	Imaging technique	Brain region
Frisoni et al. [35], 2007	EOAD vs. LOAD	EOAD (15), LOAD (15), younger healthy adults (15), older healthy adults (15)	62.5 (5.4), 78.5 (6.2), 62.5 (5.4), 76.8 (3.4)	MRI	Occipital, frontal
Frisoni et al. [116], 2005	EOAD vs. younger healthy adults	EOAD (9), LOAD (9), younger healthy adults (9), older healthy adults (17)	62 (7), 78 (4), 61 (4), 74 (6)	MRI	Temporoparietal junction
Ishii et al. [36], 2005	EOAD vs. LOAD, EOAD vs. younger healthy adults	EOAD 1st group (30), 2nd group (20), LOAD (30) (20), younger healthy adults (30) (20), older healthy adults (30) (20)	60.2 (5.2), 60.8 (4.6), 71.5 (2.6), 72.2 (3.2), 59.6 (3.8), 59.1 (2.7), 71.4 (3.5), 70.3 (4.2)	MRI	EOAD vs. LOAD: precuneus, parietal, middle temporal, fusiform gyrus; EOAD vs. younger healthy adults: medial temporal, inferior parietal, precuneus, perisylvian, basal forebrain, inferior frontal areas
Johnson et al. [38], 2001	AD vs. PS1– healthy, AD vs. PS1+ asymptomatic	PS1– healthy (23), PS1+ asymptomatic (18), PS1+ diagnosed AD (16)	42.7 (7.9), 38.1 (7.2), 51.0 (6.4)	SPECT	AD vs. PS1– healthy: posterior parietal, superior frontal; AD vs. PS1+ asymptomatic: temporoparietal
Karas et al. [117], 2007	EOAD vs. LOAD, correlational (MRI – age)	AD (51)	69 (8.5)	MRI	Precuneus
Kemp et al. [39], 2003	EOAD vs. LOAD, retrospective	EOAD (20), LOAD (44)	57.8 (4.1), 76.4 (4.5)	SPECT	Posterior association areas
Kim et al. [109], 2005	EOAD vs. LOAD	EOAD (74), LOAD (46), younger healthy adults (20), older healthy adults (13)	Onset / Exam. 55.7 (5.4), 59.1 (5.7), 69.6 (3.1), 72.8 (3.6), 56.4 (4.9), 71.5 (2.0)	PET	Superior temporal, inferior parietal, middle occipital, precuneus
Mosconi et al. [14], 2005	EOAD vs. LOAD	EOAD ApoE4– (15), EOAD ApoE4+ (12), LOAD ApoE4– (34), LOAD ApoE4+ (31), healthy adults (35)	60 (8), 65 (5), 77 (4), 77 (4), 69.3 (5.6)	PET	Orbitofrontal, inferior parietal, inferior temporal
Rabinovici et al. [40], 2010	EOAD vs. LOAD	EOAD (21), LOAD (18), healthy adults (30)	Onset / Exam. 55.2 (5.9), 60.2 (6.2), 72.0 (4.7), 77.8 (4.9) 73.7 (6.4)	PET	Temporoparietal, middle temporal, precuneus, posterior cingulate, occipital
Seo et al. [15], 2011	Correlational (age at onset – MRI)	AD (193), healthy adults (142)	73.5 (7.3), 66.0 (7.9)	MRI	Parietal
Shiino et al. [42], 2008	Correlational (age – MRI)	AD (50), healthy adults (83)	73.1 (8.7), 70.6 (6.4)	MRI	Temporal, posterior cingulate
Shiino et al. [41], 2006	Comparison of 4 subgroups of atrophy	AD (40), MCI (20), younger healthy adults (40), older healthy adults (88)	71.1 (9.7), 67.7 (9.0), 24.5 (2.1), 68.7 (8.7)	MRI	Posterior cingulate, posterior cortices

PS1+/– = Presenilin 1 mutation present/absent; ApoE4 +/– = apolipoprotein allele 4 present/absent; Exam. = examination. [a] Mean with standard deviation in parentheses.

more, continued physical activity reduces the adult-dependent decrease in adult neurogenesis [51]. Increased neurogenesis after exercise is mainly coupled with positive effects on BDNF levels, as shown in an early study [52] and supported by several studies (for reviews, see [20, 53]). Cerebral blood volume, coupling neuro- and angiogenesis, proves to be elevated in the hippocampus in healthy subjects after 3 months of aerobic exercise [54].

EOAD

Mutations in the presenilin 1 and 2 (PS1 and PS2) genes are linked to most autosomal dominantly inherited forms of EOAD. Several studies suggest an association between PS1 [55–58] and PS2 mutations [59, 60] and cell apoptosis, due to withdrawal of neurotrophins, and amyloid beta disposition [61, 62]. PS1 mutations further impair enrichment-induced neurogenesis of hippocampal neural progenitor cells [63]. Although some studies reported

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increased hippocampal proliferation in EOAD [64, 65], this hippocampal proliferation does probably not reflect neurogenesis but rather glial proliferation and vascular changes [64].

Synaptogenesis

Exercise

Animal models show that aerobic training increases synaptic development and synaptic plasticity [66, 67]. Voluntary exercise increases dendritic complexity in the dentate gyrus [47, 68] and small heat shock proteins and pre- and postsynaptic proteins in the hippocampus in rats [69]. Moderate physical activity changes the level of synaptic proteins in the motor areas of the brain and, hence, may trigger brain plasticity in these areas [70]. Apart from exercise, synaptogenesis has mainly been studied in relation to environmental enrichment. Motor learning (rotorad training) increases synapse formation in the cerebellar cortex of female rats [71–73], and acrobatic training enhances synaptogenesis in the motor cortex of male rats [74]. These synaptic changes rely on motor learning and not on the repetitive use of synapses during physical activity only [71]. Cortical levels of synaptophysin are increased after stimulation (living in cages with toys, tunnels, and a running wheel in comparison to regular cages) for 20 weeks [75].

EOAD

Research on synapses is often performed using specific synaptic vesicle proteins, such as synaptophysin and synaptotagmin [76]. The level of synaptophysin is lower in EOAD than in LOAD, indicating a higher synapse loss in EOAD [77]. In a preliminary study, synaptotagmin also seemed to be reduced in both cerebral spinal fluid and brain tissue in EOAD compared to age-matched healthy individuals [78, 79]. Greater metabolic dysfunction in the hippocampi and the basal frontal cortex, reflecting greater synapse loss, has been found in EOAD patients carrying the apolipoprotein ε4 (ApoE4) allele, compared to EOAD patients not carrying the ApoE4 allele and LOAD patients [14].

Angiogenesis

Exercise

In rats, prolonged exercise (30 days of wheel running) induces angiogenesis and increased blood flow in the cerebellum, motor cortex, and hippocampus [71, 80–82]. Angiogenesis occurs in the motor cortex within 30 days from the onset of the exercise program and these effects seem to last over time [82]. Three weeks of exercise reduces neurologic deficits and infarct volume after an induced stroke in rats – a finding that is attributed to angiogenesis [83, 84]. Elevated microvessel density is revealed in the striatum after exercise [83, 84]. Growth factors that stimulate angiogenesis are already increased after 1–3 weeks of exercise in rats, and the levels of these factors are further elevated after 3 weeks of exercise [84]. Older adults who perform regular exercise show more constant levels of cerebral blood flow in comparison to an inactive control group [85].

EOAD

Angiogenesis is hypothesized to be reduced in AD [86], but it has not been specifically studied in EOAD.

Neurotrophins

Neurotrophins are proteins that support neural networks by stimulating the development of synapses, synaptic efficiency, and survival of neurons [87]. There are several different neurotrophins, e.g. NGF, BDNF, NT-3, NT-4, and IGF-1. Neurotrophins act in brain areas with a high degree of plasticity, such as the cerebral cortex and the hippocampus [88].

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Exercise

Several animal experimental studies revealed increased BDNF levels in rats after voluntary exercise [88–94] in Ammon's horn areas (CA1 and CA4) of the hippocampus, in layers II and III of the caudal cortex, and in retrosplenial cortices [95]. Also, NGF levels are increased in the dentate gyrus, in CA4 of the hippocampus, and in layers II and III of the caudal cortex after exercise [95]. Both BDNF and NGF levels increased in the motor cortex (layer V; neuron) and in the striatum (glia) after 3 weeks of wheel running [83]. Additionally, IGF-1 levels are increased after exercise [96, 97], which is thought to be neuroprotective [98].

EOAD

Mutations in the PS1 and PS2 genes are thought to contribute to apoptotic cell death by means of trophic factor withdrawal [56, 62, 99]. PS1 mutations may alter cellular signalling systems associated with trophic factor-induced differentiation in PC12 cells [100]. This altered responsiveness to neurotrophic factors could play a role in the pathogenesis of neuritic degeneration and cell death in human PS1 mutation carriers [100]. It is also known that IGF-1 has anti-apoptotic effects. In EOAD, PS1 mutation-related apoptotic neuronal cell death may be caused by disruptions of IGF-1 signalling [101].

Cognitive Reserve

In connection with neurogenesis and exercise, the 'cognitive reserve hypothesis' has been mentioned. Cognitive reserve is thought to operate as a buffer against cognitive decline in both healthy ageing [102] and neurodegenerative processes [103]. A broad set of determinants contribute to a greater cognitive reserve [104], including exercise [6, 105, 106]. There is some inconsistency in the use of the term cognitive reserve. The literature shows a classification of cognitive reserve into more passive [107] and more active models [104]. Passive reserve is defined by quantitative neurobiological measures, such as brain volume and the number of neurons and synapses. If more neurons and synaptic connections are present, the brain is able to function longer at a normal level after neuropathological damage resulting from a neurodegenerative process has been inflicted [108]. On the other hand, active reserve implies that the brain actively attempts to cope with neuropathology. Active reserve is determined by how efficient neural networks operate in a healthy brain (neural reserve) and by the ability to compensate via cognitive strategies and the deployment of different neural networks when the pre-existing networks are damaged (neural compensation) [104]. To date, only a few studies have addressed the specific role of cognitive reserve in EOAD. Studies on the relation between passive reserve and EOAD conclude that passive reserve is lower in EOAD than in LOAD, since EOAD patients show clinical symptoms at an earlier age and therefore have a lower premorbid count of neurobiological measures [14, 77]. In contrast, studies investigating the association between active reserve and EOAD state that the degree of neuropathology at the moment of symptom onset is greater in EOAD than in LOAD. Active reserve is consequently presumed to be larger in younger than in older patients, since the younger patients are able to cope with a more severe state of neuropathology [109, 110].

Conclusions

The notion emerging from this review is that brain regions responding positively to exercise, such as frontal and parietal regions, are particularly affected in EOAD [111]. Damage in these areas results in a variety of EOAD-related clinical features, such as loss of planning

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skills, loss of initiative, and personality changes [112], which are detrimental to an individual's autonomy [113]. From this result, it follows that exercise may help fight the symptoms associated with EOAD.

Exercise leads to neurogenesis in the hippocampal formation, to synaptogenesis (particularly) in the cerebellum, to angiogenesis in the motor cortex, and to increased levels of neurotrophins. In EOAD, synapse loss and loss of neurons are neuropathological hallmarks. This suggests that exercise may partly reverse the pathological mechanisms in EOAD.

With respect to the cognitive reserve hypothesis, passive reserve is thought to be lower, and active reserve is considered to be higher in EOAD than in LOAD. Of note is that, to date, only a few studies have addressed this topic directly.

There might be a difference between EOAD and LOAD in the way these disorders respond to a treatment. This difference may be due to a variation in disease progression. Patients with EOAD show a more rapid cognitive decline than patients with LOAD [40, 114]. In a meta-analysis, AD patients with a more rapid disease progression showed greater cognitive benefit from rivastigmine treatment than slowly progressing patients [115]. The question arises whether the same may account for nonpharmacological treatments, such as exercise interventions.

This review provides theoretical support for exercise interventions in EOAD. We now present the design of an RCT currently being conducted studying the effects of exercise on the course of dementia in EOD patients.

Design of an RCT in EOD: The EXERCISE-ON Study

The EXERcise and Cognition In Sedentary adults with Early-ONset dementia (EXERCISE-ON) study is a multicentre RCT in patients with EOD (AD, vascular dementia, frontotemporal dementia, or other types of dementia). The aim of this study is to assess whether exercise slows down the progressive course of symptoms of EOD. Participants are randomly assigned to 1 of 2 exercise programs: the *aerobic exercise program* (using a bicycle ergometer) and the *flexibility and relaxation program* (flexibility and relaxation exercises). Both programs last 3 months, with a frequency of 3 times a week and are situated in a rehabilitation centre. Measurements take place at baseline, after 3 months (end of the exercise program), and after 6 months. Primary outcomes are cognitive functioning (in particular executive functioning), (instrumental) activities of daily living, and quality of life. Secondary measures include physical and neuropsychological measures. Outcome measures will be controlled for comorbid medical conditions (medical chart), depressive symptoms, ApoE genotype, and the rest-activity rhythm in view of possible moderating effects on treatment outcome.

This study is the first to assess the effect of exercise on cognition in EOD patients.

Disclosure Statement

The authors have no financial relationships or conflicts of interest to disclose.

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