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Chronic exercise in brain diseases

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Given the growing segment of the aging population, interest in lifestyle factors and interventions that may stimulate cognitive function in aging and may reduce the risk of age-related neurodegenerative disorders, such as Alzheimer's disease, is increasing. The claim that physical activity enhances brain function, that is cognitive function, and is therefore associated with a reduced risk of neurodegenerative disease is supported by different kinds of research, including observational studies, animal experimental studies and human intervention studies (Kramer and Erickson, 2007). Several epidemiological studies show a positive relationship between the level of physical activity and cognitive functioning (Fratiglioni *et al.*, 2004; Laurin *et al.*, 2001; Rovio *et al.*, 2005; Van Gelder *et al.*, 2004). In one prospective cohort study, in which participants were assessed at baseline and after five years, it was observed that physical activity of a high intensity was associated with a reduced risk of cognitive impairment, particularly in women (Laurin *et al.*, 2001). A comparable association has been reported in men. Over a 10 year time interval, longer periods of physical activity and increased intensity of the activity were associated with less decline in cognitive functioning (Van Gelder *et al.*, 2004). Physical activity does not necessarily have to be vigorous to be associated with cognition (Yaffe *et al.*, 2001). In community-dwelling older women, it was shown that those who walked most blocks a week revealed less cognitive decline (Yaffe *et al.*, 2001).

The observational nature of these epidemiological studies, however, cannot establish causation (Fratiglioni *et al.*, 2004). There have been an increasing number of intervention studies in which older people participated in a physical activity programme and cognitive measures were assessed before and after the intervention. Results of these studies have been mixed, however most studies revealed positive effects (Kramer and Erickson, 2007). A meta-analysis showed that in older people, executive functions (EF), like planning and organizing, benefited most from the physical activity intervention (Colcombe and Kramer, 2003). Only a few studies investigated the effects of the physical activity intervention on human brain

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structure. Colcombe *et al.* (2006) performed a study in which older persons participated in either an aerobic activity programme or an anaerobic activity programme (stretching and toning exercises) for six months. The aerobic activity group showed increased grey matter volume in the frontal and temporal cortices, as well as an increase in the volume of anterior white matter (Colcombe *et al.*, 2006). Compared with the relatively small number of studies examining this issue in humans, there is substantially more evidence stemming from animal experimental studies. These studies report positive effects of exercise on brain function through neurogenesis, synaptogenesis and angiogenesis (for a review see Churchill *et al.*, 2002).

In view of the beneficial effect of physical activity on brain function, that is cognitive function, there is growing interest in the possibility of physical activity being able to postpone or reverse the consequences of neurodegenerative brain diseases (Kramer and Erickson, 2007). Neurodegenerative diseases encompass a wide spectrum of clinically and pathologically heterogeneous neurological disorders (Przedborski, Vila and Jackson-Lewis, 2003). In the literature, particular interest has been given to only some neurodegenerative diseases among which Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) (Przedborski, Vila and Jackson-Lewis, 2003) are the most prominent. Studies with respect to the relationship between physical activity and cognition in neurodegenerative disease, however, have focused on dementia (mainly AD) and PD.

In this chapter, we will first describe both observational studies and physical activity intervention studies on cognition in patients with neurodegenerative disease, that is PD and dementia. Next, focus will be on cardiovascular disease since the presence of cardiovascular disease in dementia is often reported and its presence may affect the response to physical activity interventions. Within the scope of vascular disease, the role of nitric oxide (NO), a potent vasodilator, will also be discussed. In neurodegenerative disease, NO metabolism is disrupted, which may influence the response to physical activity. Therefore, the relationship between cardiovascular disease, NO and physical activity in neurodegenerative disease will be discussed. Finally, some recommendations concerning physical activity interventions in older people with neurodegenerative disease will be given.

15.1 Observational studies of physical activity

Epidemiological studies concerning the relationship between physical activity and the occurrence of PD show inconsistent results. In one study, physical activity appeared to be negatively associated with early onset PD, particularly in the presence of head trauma (Tsai *et al.*, 2002). A retrospective study revealed that regular exercise during teenage years was associated with a lower risk of PD, but this association did not turn out to be significant (Sasco *et al.*, 1992). In this study, the relationship between physical activity and PD seemed to be dependent on the level of exercise

participation. More specifically, engagement in a moderate amount of sports in adulthood was significantly associated with a reduced risk for PD, whereas participation in heavy sports was not (Sasco *et al.*, 1992). Another study that retrospectively determined level of physical activity during lifetime did not reveal differences between PD patients and healthy controls before the first symptoms of PD appeared (Fertl, Doppelbauer and Auff, 1993). Not surprisingly, after disease onset a marked decrease in engagement of physical activity was noticed (Fertl, Doppelbauer and Auff, 1993). In all of these studies, physical activity was determined retrospectively and all had relatively small sample sizes. A prospective cohort study showed that higher levels of physical activity before PD symptom onset were negatively associated with the risk for PD in men, but not in women (Chen *et al.*, 2005). This finding may be interpreted in two different ways: either higher levels of participation in physical activity may reduce the risk of PD in men or men predisposed to PD may have avoided strenuous exercise in the past (Chen *et al.*, 2005). Another recent prospective cohort study also did not find convincing evidence to support the hypothesis that engagement in physical activity (walking, stair climbing and sports activities) reduces the risk of PD (Logroscino *et al.*, 2006). Taken together, results concerning the relation between physical activity and risk of PD remain elusive.

Several studies have described the association between physical activity and the risk of AD. Prospective studies revealed a reduced risk of AD in individuals showing the highest level of physical activity (Abbott *et al.*, 2004; Larson *et al.*, 2006; Rovio *et al.*, 2005). One prospective study with a follow-up period of 21 years showed that the people engaging in physical activity at least twice a week during midlife had a lower risk of developing AD (Rovio *et al.*, 2005). With respect to the question, what aspect of physical activity is particularly associated with a delay in AD onset, it was shown that the number of different activities may be even more important than frequency or duration of the activity (Podewils *et al.*, 2005). Although the majority of epidemiological studies show a negative relationship between levels of physical activity and risk of AD, not all studies report such a relationship (Verghese *et al.*, 2003).

Most observational studies examining the relationship between level of physical activity and risk for dementia have focused on AD. Some studies also included other sub-types of dementia such as vascular dementia (VaD) (Lindsay *et al.*, 2004; Podewils *et al.*, 2005). Although the most important risk factors for VaD are cardiovascular risk factors (Román, 2005), and the benefits of physical activity on the cardiovascular condition are well known (Casillas *et al.*, 2007), studies investigating the association between physical activity and VaD reveal inconsistent results. In some studies, physical activity is associated with a reduced risk of VaD (Lindsay and Anderson, 2004; Podewils *et al.*, 2005), whereas this relationship has also been less apparent (Abbott *et al.*, 2004) or even absent (Verghese *et al.*, 2003). All in all, the majority of epidemiological studies report an association between level of physical activity and a decreased risk of dementia (e.g. AD), but some studies do not (Verghese *et al.*, 2003; Wang *et al.*, 2002). In one of these studies, however, the variables describing the level of physical activity were restricted to swimming, walking and

gymnastics. The authors state that only some people pursued these activities, rendering the power of the analysis to detect an association limited (Wang *et al.*, 2002). In another study (Verghese *et al.*, 2003), a positive association between a calculated 'physical activity score' for all types of activity and cognition was not found. However, a relationship between dancing and cognition was shown. Other physical activities, such as playing tennis or golf, could not be included in the 'physical activity score' since too few people engaged in those activities. Therefore, of the remaining activities, the dancing activity may have been one of the highest intensity, and the level of intensity appears to be associated with cognition (Scherder *et al.*, 2007b). As mentioned earlier, epidemiological studies do not provide information on the causality of the association, therefore in the next section, intervention studies will be discussed (for detailed information on the clinical intervention studies, see Table 15.1).

15.2 Physical activity intervention studies

Physical activity, cognition and Parkinson's disease

Animal experimental studies did reveal positive effects of physical activity on symptoms of PD. In animal models of PD, treadmill running induced a reduction in dopamine depletion in the striatum compared with control animals (Poulton and Muir, 2005) and resulted in the attenuation of behavioural and motor deficits (Tillerson *et al.*, 2003). In a PD rat model, forced exercise resulted in an increase in glial-derived neurotrophic factor (GDNF) which protects dopaminergic neurons (Cohen *et al.*, 2003). Additionally, wheel running activates the dopaminergic system and leads to enhanced levels of dopamine in the striatum (Hattori *et al.*, 1996).

Results from intervention studies in humans on the effects of physical activity on cognition are inconclusive. One exercise intervention study in PD patients combined physical therapy with motor imagery practice (Tamir, Dickstein and Huberman, 2007). Twenty-one PD patients completed a physical therapy programme of one hour, twice a week, over 12 weeks. Physical activities included callisthenics, practice of specific motor function, for example transfer skills, and relaxation exercises. The experimental group also performed motor imagery practice before and after the execution of the movements. Although the experimental group showed higher mean scores after the treatment on the cognitive measures, neither group showed a significant improvement in cognition. Another study offered an intensive twice a week exercise programme to PD patients for 14 weeks (Reuter *et al.*, 1999). One session took an hour and was performed once a week in the water, while the other session took place in a gymnasium. Participants were assessed at baseline, after 7, 14 and 20 weeks. Cognition, measured by a sub-scale of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn and Elton, 1987) and a measure for global cognitive functioning, the Mini-Mental State Examination (MMSE) (Folstein, Folstein and McHugh, 1975), did not show significant changes during the entire

Table 15.1 Clinical intervention studies. Characteristics of studies examining the effects of physical activity on cognition in patients with neurodegenerative brain disease.

Study	Sample [men/women]	*N*	Age	Design	Type of Intervention	Dependent Variables	Results
Studies in PD patients							
Baatile *et al.*, 2000	Veterans with PD Severity of disability stage 2 or 3 according to the Hoehn and Yahr scale (1967)	6	$M = 72.7$	Single group; repeated measures	Pole striding training, three times a week for 37 ± 3 min for 8 wks	Standardized interviews concerning the severity of PD and quality of life.	4 out of 6 participants showed an improvement on the interviews, also on the cognitive dimension
	[6/0]		SD = 3.7				
Reuter *et al.*, 1999	Patients with idiopathic PD (UK-PDSBB criteria; Hughes *et al.*, 1992). Severity of disability ranging from 2 to 4 according to Hoehn and Yahr (1967)	16	$M = 65.4$	Single group; repeated measures	Twice a week training programme for 1 hr over 14 wks. Once a week water exercises and once a week exercises in a gymnasium including gait exercises and strength training	Rating scales for PD-specific motor disability, sport-specific disability MMSE, mood and sickness impact profile.	No significant change in cognition was found. Motor disability, mood and subjective well-being improved
	[9/7]		SD = 5.9				

(*continued*)

Table 15.1 (*Continued*)

Study	Sample [men/women]	*N*	Age	Design	Type of Intervention	Dependent Variables	Results
Tamir, Dickstein and Huberman, 2007	Community-dwelling patients with idiopathic PD. Severity of diasability between stages 1.5–3 according to Hoehn and Yahr (1967)	21	$M = 67.4$	Exp group/control group; repeated measures randomized procedure	Experimental group: combination of imagery and physical practice	Performance of movement sequence, balance functions, neurological and functional deficits, cognitive ability. Test administration was blinded	The experimental group showed higher gains in mental and motor tasks, but these gains were not significant
	[15/8]		SD = 9		Control group: only physical practice Physical practice in both groups included callisthenics, training of motor function, relaxation exercises. Sessions took 1 hr and were held twice a wk for 12 wks		
Studies in AD patients							
Arkin, 2001	Community-dwelling AD patients and nursing-home residents with AD	11	$M = 79$	Single group; repeated measures	Twice weekly physical fitness training of increasing duration for a mean of 30 min for 2 × 10 wks,	Neuropsychological tests	Performance on several cognitive tasks was maintained. Fitness and mood gains were obtained

	(NINCDS-ADRDA) MMSE: M = 23 (15–29) [3/8]		(59–86)			Mood questionnaires	
Arkin, 2003	Community dwelling AD patients (NINCDS-ADRDA)	24	M = 78.8	Single group; repeated measures	As for Arkin 2001, plus 10 recreational sessions	Neuropsychological tests (no details provided)	Cognitive decline was slowed and mood improved. Not further specified
	MMSE: 15–29 [8/16]		(SD = 8)			Mood questionnaires	
Cott *et al.*, 2002	Nursing-home residents with a medical diagnosis of AD	74	M = 82	Exp group/2 control groups; repeated measures Randomized procedure	Exp group: walking and talking in pairs for 30 min, 5 d a wk for 16 wks	Communication measures (administration was blinded)	No change in communication
	30 intervention		SD = 8		Social visit control group: conversation while sitting in pairs, in the same frequency	Ambulation, functional status (mental disorganization or confusion, physical disability, socially irritating behaviour and disengagement) (administration was not blinded)	No change in ambulation
	25 social visit control				Control group: no study-provided intervention		No change in functional status

(*continued*)

Table 15.1 (*Continued*)

Study	Sample [men/women]	*N*	Age	Design	Type of Intervention	Dependent Variables	Results
	19 control MMSE: Exp group I: M = 6.2; Exp group II: M = 5.4 Control group: M = 6.3 [35/39]						
Friedman and Tappen, 1991	Nursing home residents with probable AD (NINCDS-ADRDA criteria and MMSE scores < 19) MMSE: Exp group: M = 6.5; Control group: M = 6.4 [17/13]	30	M = 72.8 (60–87)	Exp group/control group; repeated measures randomized procedure	Exp group: 30 min walk 3 times a week for 10 wks Control group: conversation only in the same frequency	Communication scales. Administration was not blinded but inter-rater reliability was checked	Improvement in communication in the experimental group. Conversation only did not result in a significant improvement
Lindenmuth and Moose, 1990	People with AD	43	M = 82.8	Exp group/control group; repeated measures	Exp group: somatic and isotonic-relaxation exercises for 8 wks	Cognitive Abilities Screening Test. Unclear whether test administration was blinded	Experimental group showed significant improvement

	[27/16]		(65–98)	No randomized procedure	Control group: no intervention		
Palleschi *et al.*, 1996	Males diagnosed with possible AD (NINCDS-ADRDA criteria, MMSE: 18–21	15	M = 74.0	Single group; repeated measures	Exercise on an exercise cycle (heart rate at +/− 70% of max pulse rate)	Test of attentional matrix, verbal span tests, MMSE	Significant improvement on all tasks
	[0/15]		SD = 1.5		20 min exercise 3 d a wk, for 3 mo		
Rolland *et al.*, 2000	People with probable AD (NINCDS-ADRDA criteria)	23	M = 78	Single group; repeated measures	Endurance exercise: walking, exercise cycle for 5–12 wks (M = 7) for 35 min (10–80 min)	Scales for (Instrumental) Activities of Daily Living; MMSE; behavioural questionnaire; nutritional assessment; test for balance	Improved nutritional status, improved cognitive function, improvement in behavioural problems
	[13/10]		(71–92)				
Studies in 'dementia'							
Baum *et al.*, 2003	Frail long-term care-facility residents	20	M = 88	Exp group/control group; repeated measures	Exp group: exercise programme containing seated strength and range of motion exercises	MMSE and physical function measures. Test administration was blinded	Increased MMSE score and physical function improved
	MMSE: Exp group M = 21; control group M = 22		(75–99)	Randomized procedure	Control group: recreational therapy		
	(10–29)				1-hr sessions, 3 times a wk, during 6 mo		

(*continued*)

Table 15.1 (*Continued*)

Study	Sample [men/ women]	*N*	Age	Design	Type of Intervention	Dependent Variables	Results
De Carvalho Bastone and Filho, 2004	Nursing home residents	37	Exp group M = 76.8	Exp group/Control group; repeated measures	Exp group: exercise programme including mobility exercises, strengthening exercises and walking	MMSE, mood questionnaire, functional performance tests. Unclear whether test administration was blinded	Maintenance of MMSE score compared with the control group. Improvement of mood and physical performance
	MMSE: Exp group		Control group	No randomized procedure	1 hr, once a wk, for 6 months		
	M = 19.2; Control group		M = 80.3		Control group: no study-provided intervention		
	M = 20.9		(60–99)				
Hopman-Rock *et al.*, 1999	Nursing home residents	92	Exp group M = 83.8 (SD = 5.8)	Exp group/control group; repeated measures randomized procedure	Exp group: twice weekly 'psychomotor activation (PAP)' for 45 min over 6 months. PAP consists of sporting activities, games and hobby activities	Cognitive screenings test ($n = 61$, test administration was blinded) and behavioural questionnaires (unclear whether administration was blinded	
	Stabilized cognitive function in the PAP group and increased positive group behaviour in those with mild problems						

	45 intervention 47 control Cognitive screening test-20: Exp group: M = 5.1; Control group: M = 6.1		Control group M = 84.2 (SD = 5.6)		Control group: no study-provided intervention		
McMurdo and Rennie, 1994	Nursing-home residents MMSE: Exp group M = 15.7; Control group M = 15.2	55	M = 83 (67–98)	Exp group/control group; repeated measures Randomized procedure	Exp group: seated exercises to music Control group: reminiscence therapy All sessions for 45 min, twice weekly, for 6 months	MMSE, reaction time and physical function measures. Unclear whether test administration was blinded	No improved performance on the MMSE. No improved reaction time. Improvement of physical function in both groups
Mulrow *et al.*, 1994	Nursing home residents	180	Exp group	Exp group/control group; repeated measures.	Exp group: three times a week exercise to music training, containing range-of-motion exercises, balance, transfer and endurance training for 30–45 min, for 4 months	MMSE, mood questionnaire, physical function measures, ADL scale. Test administration was blinded accept for ADL	Performance on the MMSE did not improve. No change in feelings of depression. No change in ADL. Small increase in physical function

(*continued*)

Table 15.1 (*Continued*)

Study	Sample [men/ women]	*N*	Age	Design	Type of Intervention	Dependent Variables	Results
	MMSE: M = 21		M = 79.7 (SD = 8.5) Control group M = 81.4 (SD = 8.5)	Randomized procedure	Control group: social visits with the same frequency		
Powell, 1974	Geriatric mental patients	30	M = 69.3 (59–89)	Two treatment groups/control group; repeated measures Randomized procedure	Exercise intervention I: 1 hr a day, 5 d a wk exercise therapy, involving walking and callisthenics, for 12 wks, Social therapy intervention: Arts and crafts work, music therapy and games playing in the same frequency Control group: No study-provided intervention	3 cognitive tests, 2 behavioural questionnaires Unclear whether test administration was blinded	Cognition improved, behavioural problems increased

ADL = activities of daily living; Exp = experimental; hr = hour; M = mean; min = minutes; MMSE = Mini Mental State Examination; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; SD = standard deviation; wk = week.

Van de Winckel *et al.*, 2004	Female patients with dementia living in a psychiatric hospital	25	Exp group M = 81.33 (SD = 4.2)	Exp group/Control group; repeated measures	Exp group: Daily 30 min seated exercise programme, containing upper and lower body strengthening, balance, trunk movements and flexibility straining, supported by music for 3 months	MMSE, dementia screenings test including measures of memory and word fluency (administration was not blinded), behavioural questionnaire (administration was blinded)	Improved score on the MMSE and a verbal fluency task. No change in behaviour
	MMSE: Exp group M = 12.9; Control group M = 10.8		Control group M = 81.9 (SD = 4.2)	Randomized procedure	Control: daily conversation in the same frequency		

AD = Alzheimer's disease; ADRDA = Alzheimer's Disease and Related Disorders Association; hr = hour; M = mean; min = minutes; MMSE = Mini Mental State Examination; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; PD = Parkinson's disease; SD = standard deviation; UK-PDSBB United Kingdom Parkinson's Disease Society Brain Bank; wk = week; Exp = experimental; ADL = activities of daily living

study period (Reuter *et al.*, 1999). A limitation of the study was the lack of a control group. In a small study, six male PD patients engaged in a training programme for eight weeks (Baatile *et al.*, 2000). The programme focused on a polestriding activity, that is a walking activity with the use of poles in a similar way to cross country skiing. Training took place three times a week for one hour. After the intervention programme, four out of the six patients showed a higher score on a self-administered survey measuring cognition. In view of the limited sample size and lack of a control group, results should be interpreted with caution.

All in all, there is a paucity in physical activity intervention studies in PD patients that focus on cognition and the assessment of cognitive functions is limited. The few studies that did investigate this issue do not report significant positive findings or are characterized by methodological shortcomings.

15.3 Physical activity, cognition and different types of dementia

The four most common sub-types of dementia are AD, VaD, dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD) (Bastos Leite, Scheltens and Barkhof, 2004). Effects of exercise on cognition in these four major sub-types of dementia are discussed below. Unfortunately, many physical activity intervention studies did not specify the sub-type of dementia of the participants, but will be reviewed here as well.

Alzheimer's disease

In an AD mouse model, wheel running activity initiated up-regulation of hippocampal brain-derived neurotrophic factor (BDNF) and hippocampal neurogenesis (Wolf *et al.*, 2006). One study, using a mouse model of AD, showed that pathology characteristic of AD, amyloid plaques, were significantly reduced after voluntary wheel running for one month (Adlard *et al.*, 2005). These findings were confirmed in another study that examined AD mice living in either an enriched environment or in standard cages (Lazarov *et al.*, 2005). Mice that lived in the enriched environment and had access to running wheels showed a reduced amyloid burden (Lazarov *et al.*, 2005). In contrast, another study showed that the AD mice that lived in the enriched environment showed increased amyloid load (Jankowsky *et al.*, 2003). However, the enriched environment condition showed a lower number of running wheels, which limited the opportunity to run and may have led to competition and stress (Lazarov *et al.*, 2005).

There have been some intervention studies that examined the effects of a physical activity programme on AD patients. Some studies offered an intervention programme that offered a form of physical activity only ('exclusively physical activity'), whereas other studies offered a form of physical activity combined with another type of stimulation, for example music, rendering conclusions on what type of intervention was (most) beneficial impossible. Therefore, these studies will be described separately.

Exclusively physical activity

Only a few studies have implemented exercise programmes in studies that included AD patients. In one study, a group of 23 moderate to severe AD patients participated in a programme of endurance exercise that consisted of walking and riding an exercise cycle for a mean of seven weeks (5–12 weeks) (Rolland *et al.*, 2000). After the intervention, they showed significantly improved performance on a measure of global cognitive functioning, the MMSE. The time the patients participated in the daily activity programme varied considerably, from 10 to 80 min. Another study offered an exercise programme consisting of riding on an exercise cycle for more than 20 min a day, three days a week for three months to 15 males with possible AD. Following the intervention, they showed an improvement in their performance on three tests of attention and short-term memory and the MMSE (Palleschi *et al.*, 1996). It is noteworthy, however, that a control group was lacking in both of the aforementioned studies. Finally, one study reports positive effects on cognition after an eight week exercise programme that included somatic and relaxation exercises. The precise nature of the cognitive abilities was unfortunately not further specified (Lindenmuth and Moose, 1990). Also, the participants were allowed to choose whether they preferred to be in the experimental or control group. Moreover, participation in the exercise group was irregular and the control group did not take part in any alternative activity.

In sum, all three studies that included AD patients report an improvement in global cognitive functioning after participation in an exercise programme. Nevertheless, these results should be interpreted with caution, in view of the methodological flaws.

Physical activity combined with another type of intervention

In a pilot study, 11 patients with mild to moderate AD followed a twice-weekly physical fitness training programme, containing a variety of exercises, such as aerobic and weight resistance activities, for 10 weeks (Arkin, 2001). Seven out of the 11 participants also received specific memory and language stimulation exercises, for example playing word games. The study suggested that the exercise prevented a significant cognitive decline in the participants, regardless of whether the participants had received memory and language training. The small sample size and lack of a nonexercise control group are limitations of the study. In a longitudinal follow-up study, a comparable exercise programme, adding 10 recreational activity sessions, was followed by 24 patients with AD during a period of one to four years (Arkin, 2003). Results suggest the slowing of cognitive decline. Unfortunately, details concerning the cognitive benefits were not provided. Moreover, a control group was lacking. Two studies did offer randomized controlled trials and examined the effects of walking combined with talking on communication skills in AD patients. The results of the two studies were conflicting. Thirty moderate to severe AD patients were randomly allocated to two groups: the experimental group, which received a 30 min walking and conversation programme, and a control group that received a 30 min conversation-only programme (Friedman and Tappen, 1991). After the

10 week treatment period, communication improved only in the group that was offered walking combined with conversation. These results were not confirmed in another study, in which 90 AD patients were randomly assigned to three groups: a walking and conversation group, a conversation-only group and a nonintervention control group (Cott *et al.*, 2002). The interventions were applied for 30 min, five days a week for 16 weeks. Social communication skills and communication of basic needs were not found to be improved after the intervention period in the walking and conversation group compared with the other two groups. Notably, the participants demonstrated large differences in level of cognitive impairment at baseline, but most showed severe cognitive impairment. The participants may have been too severely cognitively impaired to benefit from the intervention (Cott *et al.*, 2002).

In sum, studies including AD patients that investigated the effects of a physical activity intervention in combination with another type of stimulation have shown inconsistent results. The inconsistency in findings may be attributed to differences in study design or the stage of dementia of the participants.

Vascular dementia, dementia with lewy bodies and frontotemporal dementia

As far as the authors know, studies examining the effects of physical activity on cognition have not been performed with respect to VaD, DLB and FTD.

Older persons with 'dementia'

Exclusively physical activity

Thirty psychogeriatric patients were allocated at random to a group that received exercise therapy, a group that received conventional social therapy or a nonintervention control group (Powell, 1974). Both interventions were offered five days per week and lasted an hour. After 12 weeks of treatment, only the exercise group showed improved performance on tasks that appeal to logical reasoning and memory. In a more recent study (De Carvalho Bastone and Filho, 2004), 40 people living in a nursing home were assigned to either an exercise group or a nonintervention control group. The exercise programme, which involved walking, mobility exercises and strength training was offered twice a week for one hour. After six months, performance on the MMSE was maintained in the exercise group, whereas the performance on the MMSE deteriorated significantly in the control group. Lack of a randomized procedure is a limitation of the study. In another study (Baum *et al.*, 2003), 20 frail, long-term care-home residents participated and were randomly assigned to two groups. One group received an exercise programme containing seated range of motion (ROM) exercises and strength training for one hour, three times per week and the other group received recreational therapy with the same frequency. After six months, performance on the MMSE improved significantly only in the group that attended the exercise programme. In contrast, in a study in which 189 frail, nursing-home residents participated (Mulrow *et al.*, 1994), performance on the MMSE was not

found to be improved after four months of physical therapy. In this study, the nursing home residents were randomly divided to either physical therapy sessions or friendly visits for three times a week. Physical therapy involved ROM exercises, resistance exercises, endurance activities and gait training.

In sum, the effects on cognition in studies offering exercise programmes in nursing-home residents have been inconsistent.

Physical activity combined with another type of intervention

Fifteen women with dementia participated in an exercise programme, which consisted of daily seated exercises supported by music (Van de Winckel *et al.*, 2004). The control group, which consisted of 10 patients, received conversation with the same frequency. Compared with the control group, the exercise group showed a significant improvement on the MMSE and a verbal fluency measure after three months. These beneficial effects were, however, not confirmed in another randomized controlled study that offered a comparable intervention. Sixty-five older nursing-home residents were randomly assigned to either a seated exercise to music intervention or a reminiscence intervention offered twice-weekly, for 45 min over 6 months. Neither group showed improved reaction time or improved MMSE score after the intervention period (McMurdo and Rennie, 1994). In a randomized controlled study, including people with dementia, the effects of a psychomotor activation programme (PAP) were investigated. This programme was offered twice a week and involved sporting activities, games and hobby activities in order to stimulate cognitive and psychosocial functioning. Sixty-one nursing-home residents with dementia completed either the PAP programme or attended no specific intervention but took part in their regular activities. Results indicated that the residents that participated in the PAP programme maintained their global cognitive functioning, whereas the control group deteriorated (Hopman-Rock *et al.*, 1999).

In sum, results of studies investigating the effects of a combination of physical activity with another type of stimulation with older people living in long-term care facilities show inconsistent results. It is noteworthy that in all the above-mentioned studies on residents of long-term care facilities, the residents generally appeared to be cognitively impaired, but whether *all* participants were cognitively impaired remains elusive.

Overall conclusion

Most studies concerning the effects of physical activity on cognition in neurodegenerative diseases have focused on patients with AD or 'dementia', and only a handful on patients with PD. Some studies are characterized by serious methodological flaws such as small sample sizes (Arkin, 2001; Baatile *et al.*, 2000), the lack of a control group (Arkin, 2003; Palleschi *et al.*, 1996; Reuter *et al.*, 1999; Rolland *et al.*, 2000), no randomized procedure (De Carvalho Bastone and Filho, 2004; Lindenmuth and Moose, 1990) and unblinded test assessment or no clarity to it (Friedman and

Tappen, 1991; McMurdo and Rennie, 1994; Powell, 1974). In addition, where physical activity has been combined with another type of activity, beneficial effects cannot be purely attributed to the exercise performed. Apart from these flaws, results of the studies have been inconsistent. A number of factors may be responsible for these inconsistent findings, for example the role of physical activity duration, intensity and frequency, and the cognitive functions examined in the studies (Kramer and Erickson, 2007). However, characteristics of the participants may also play an important role, especially age, gender, differences in the stage of the disease, brain areas and molecular factors most affected, and co-morbidity of diseases (Kramer and Erickson, 2007; Scherder *et al.*, 2007a). It will be important for future research to characterize the people that will benefit most and those that will benefit least from a physical activity intervention.

15.4 Role of vascular disease

One type of co-morbidity frequently present in older people with dementia is vascular disease, that is hypertension (Wolozin and Bednar, 2006). It is suggested in this chapter, that the presence of vascular disease may particularly moderate the effect of physical activity on cognition in some older people with neurodegenerative disease (Eggermont *et al.*, 2006; Scherder *et al.*, 2007a). This may sound somewhat counter-intuitive, since cardiac patients generally are advised to exercise (Casillas *et al.*, 2007). However, in the present chapter, we will describe how exercise may benefit cognition in neurodegenerative disease, but how vascular disease may disrupt cerebral autoregulation and hence the ability of physical activity to stimulate cerebral blood flow.

Vascular disease and cerebral hypoperfusion have been reported in different types of neurodegenerative disease. Hypoperfusion in PD has been reported in parieto-temporo-occipital cortex, dorsolateral prefrontal cortex, cingulate gyrus and insula (Hsu *et al.*, 2007). In addition, reductions in regional cerebral blood flow in the left temporo-parietal region discriminated PD patients with dementia from PD patients without (Derejko *et al.*, 2006). Vascular disease in PD may even show a synergistic effect on cognitive decline (Demirkiran *et al.*, 2001).

Vascular disease has also been reported in different sub-types of dementia. There is growing support for the notion that AD may have a vascular basis (De La Torre, 2002). Besides the similar risk factors for cardiovascular disease and AD, among which are hypertension, atherosclerosis and diabetes (De La Torre, 2002), evidence from AD mouse models and reports on severe reduction in cerebral blood flow (CBF) confirm the contribution of vascular factors to AD (Iadecola, 2004). In addition, abnormalities in the brain microvascular system are frequently reported in AD (Farkas and Luiten, 2001). Impairment in cognition can be the result of dysfunctioning of blood vessels through impaired nutrient transport to neurons and impairment in amyloid-β (Aβ) clearance from the brain (Iadecola, 2004). Indeed, the relationship between Aβ deposition and cerebrovascular disease may lead to a

vicious circle in AD pathology: while Aβ produces cerebrovascular dysregulation and an increase in the susceptibility of the brain to cerebral ischaemia, ischaemia in turn stimulates the amyloid precursor protein (App) and Aβ cleavage (Iadecola, 2004). Aβ-induced cerebrovascular dysfunction might also reduce blood flow sufficiently to produce ischaemic injury (Iadecola, 2004). Due to disturbance of cerebrovascular autoregulation, the sub-cortical white matter is highly susceptible to infarction, which may provide an explanation for the frequently observed white matter infarcts in AD (Barber *et al.*, 1999). Another important feature of AD is the formation of cerebral amyloid angiopathy (CAA) which constitutes a combination of pathology typical for AD (amyloid) and vascular pathology (angiopathy). CAA results from the deposition of protein, among which is the Aß-precursor protein, in the cerebral blood vessel walls (Castellani *et al.*, 2004). CAA can lead to ischaemia and haemorrhage, which aggravates the course of AD (Castellani *et al.*, 2004).

With respect to VaD, the common causal element is cerebrovascular disease. The main risk factors of VaD are advanced age, hypertension, diabetes, smoking, hyperhomocysteinaemia and hyperfibrinogenaemia, (Román *et al.*, 2002). The presence of hypertension particularly increases the risk of VaD (Posner *et al.*, 2002). Hypertension and other cardiovascular risk factors can lead to arteriosclerosis which, in turn, can cause cerebral infarction (Román *et al.*, 2002). Other conditions that can result in cerebral hypoperfusion are risk factors for VaD as well, among which obstructive sleep apnoea, congestive heart failure, cardiac arrhythmias and orthostatic hypotension are prominent (Román, 2005). Studies measuring reduction in cerebral perfusion in DLB patients reveal mainly frontal lobe hypoperfusion compared with AD patients (Defebvre *et al.*, 1999; Kasama *et al.*, 2005). In addition, besides hypoperfusion in the lateral parietal and temporal regions and the precuneus (Mito *et al.*, 2005; Shimizu *et al.*, 2005), marked hypoperfusion in the occipital regions has been reported in DLB (Ceravolo *et al.*, 2003; Hanyu *et al.*, 2006; Shimizu *et al.*, 2005). White matter abnormalities have been reported in the parietal, frontal and occipital regions (Bozzali *et al.*, 2005), however presence of white matter hyperintensities (WMH) did not differ between controls in another study (Burton *et al.*, 2006). Nonetheless, people with DLB frequently present with neurocardiovascular instability, such as orthostatic hypotension (Kenny, Kalaria and Ballard, 2002), which, in turn, has been associated with increased WMH (Ballard *et al.*, 2000).

Support for a vascular involvement in the pathogenesis of frontotemporal lobar degeneration (FTLD) comes from several studies revealing a marked cerebral hypoperfusion in the affected regions (frontal and temporal areas) (Diehl-Schmid *et al.*, 2007; Du *et al.*, 2006; Hodges, 2001). In frontal variant FTD (fvFTD), the exact location of hypoperfusion in frontal and temporal areas seems to be dependent on the behavioural features, such as inertia and disinhibition (Le Ber *et al.*, 2006). Further evidence for vascular involvement stems from another study, in which degenerating astrocytes in FTD were inversely correlated with cerebral perfusion (Martin *et al.*, 2001). Since astrocytes have been shown to degenerate in response to hypoxia and ischaemia, it is speculatively suggested that the reduced cerebral perfusion has a causal role in disease progression via ischaemic or hypoxic insult (Martin *et al.*, 2001). Finally, white

matter changes are already present in an early stage of both fvFTD and temporal variant FTD (tvFTD) (Borroni *et al.*, 2007).

In sum, in all types of dementia and in PD (especially in those with dementia), cerebrovascular disease and cerebral hypoperfusion have been reported. Since in the regulation of cerebral blood flow, NO, a potent vasodilator, plays a crucial role (Furchgott, 1996), NO regulation in neurodegenerative disease and exercise will be discussed.

Levels of nitric oxide in neurodegenerative disease

NO is derived from vascular endothelial nitric oxide synthase (eNOS) and plays a crucial role in the cerebral perfusion by influencing vascular tone, blood pressure and vascular homeostasis (Eggermont *et al.*, 2006; Huang *et al.*, 1995; Kubes and Granger, 1992). NO mediates cerebral autoregulation (White, Vallance and Markus, 2000) and protects endothelial cell function (Maxwell, 2002). NO is involved in the pathogenic processes in various neurodegenerative diseases (Zhang, Dawson and Dawson, 2006). How NO specifically contributes to these diseases remains elusive, however progress has been made on our understanding of the role of NO in PD and other neurodegenerative diseases (Boje, 2004). Both post-mortem studies on PD brains and studies with PD mouse models lend support to a role of NO in the pathogenic process (Zhang, Dawson and Dawson, 2006). Disruption of NO levels in AD is recognized to contribute to the pathogenesis in AD (Corzo *et al.*, 2007). It has been suggested that cerebral hypoperfusion in AD disturbs NO metabolism, which in turn causes vascular injury (Cooke and Dzau, 1997). More specifically, it is suggested that when the cerebral perfusion is reduced to a certain threshold, NO levels are up-regulated to maintain vascular homeostasis (De La Torre, 2002). In failing to do so, NO levels become even more disrupted which may damage the endothelial cells and impair glucose transport to the brain (Chen *et al.*, 1999). NO is also known to play a role in the pathogenesis of VaD (Corzo *et al.*, 2007). Levels of NO have been shown to be reduced (Corzo *et al.*, 2007). In contrast, it has also been reported that NO levels do not differ between VaD patients, AD patients and healthy controls (Folin *et al.*, 2005). A possible explanation for these conflicting results could be that NO levels differ between sub-types of dementia, that is Binswanger's disease and multiple small infarct type (Tohgi *et al.*, 1998), and depend on the stage of dementia (Tohgi *et al.*, 1998). Also patients with dementia with DLB show microvasculopathy and impaired NO release (Katsuse, Iseki and Kosaka, 2003; Togo, Katsuse and Iseki, 2004).

It can be concluded that vascular disease and nitric oxide appear to be involved in neurodegenerative disease.

Nitric oxide metabolism and physical activity

There is a relationship between NO, cerebral perfusion and physical activity, that is exercise. In animal experimental studies, NO release is increased by exercise,

especially in the hippocampus (Endres *et al.*, 2003). Enhanced NO leads to vasodilatation and consequently to increased cerebral perfusion, which may improve cerebrovascular function (Kubes and Granger, 1992). In addition, tissue-type plasminogen activator (t-PA), which is released by NO, (Schini-Kerth, 1999), is also elevated after physical activity (Smith *et al.*, 2003). t-PA is an enzyme that converts plasminogen – an active proenzyme (Lijnen and Collen, 1997) – into plasmin (Melchor, Pawlak and Strickland, 2003), which in turn reduces fibrin clots in the circulation. Therefore, t-PA plays a pivotal role in the prevention of thrombosis (Muldowney and Vaughan, 2002). An enhancement of t-PA levels by exercise may improve endothelial fibrinolytic function (Smith *et al.*, 2003).

In sum, cerebral hypoperfusion may be ameliorated by exercise by means of NO and t-PA enhancements.

15.5 Neurodegenerative disease, nitric oxide, vascular disease and physical activity

As described earlier, several types of neurodegenerative disease show disruptions in NO metabolism. NO levels may be even more affected in cases of cardiovascular disease, causing additional damage to the endothelium (Valgimigli *et al.*, 2003). It is suggested, in this chapter, that increased physical activity may not necessarily be beneficial under all circumstances. More specifically, attention should be paid to cases that show neurodegenerative disease in combination with cardiovascular disease. Notably, increased plasmin levels by enhanced t-PA release may also reduce the level of laminin (Chen and Strickland, 1997), a protein that decreases neurotoxicity in AD (Morgan and Inestrosa, 2001) and protects dopaminergic neurons in PD (Väänänen *et al.*, 2006). Particularly in the presence of ischaemic lesions, plasmin degrades laminin and can cause neuronal damage (Wang *et al.*, 1998). In other words, (high-intensity) physical activity may lead to laminin depletion and hence to neuronal damage. It is, therefore, of great importance to maintain the laminin concentration at physiologically normal levels. Moreover, in patients with a reduced cardiac output resulting from cardiac disease, the blood supply to the large muscle cells may preclude increased cerebral blood flow (Koike *et al.*, 2004). The positive effects of exercise on cerebral perfusion, therefore, appear to rely on the presence of cardiovascular risk factors and the patient's cardiac condition.

15.6 Final conclusion

In this chapter, we have summarized that all the major sub-types of dementia show cerebrovascular disease. In view of the aforementioned risk of, for example, ischaemic lesions, it is suggested that physical activity in older people with neurodegenerative disease should not be prescribed light-heartedly, but under conditions

involving careful medical screening and close monitoring. It is recommended in future research on the effects of physical activity in older people with neurodegenerative disease that one should control for co-morbid vascular disease and cardiovascular risk factors. These risk factors might attenuate or undo beneficial effects of exercise on cognition, or may even pose a risk for the patient in exercise. In conclusion, participation in exercise in addition to one's usual physical activities may not be beneficial in all cases of neurodegenerative disease. A take-home message with respect to exercise in neurodegenerative disease may thus be: 'more is not necessarily better'.