CHAPTER 8

Summary and general discussion

The main aims of this thesis were 1) to increase insight into the relationship between the level of physical activity and executive functioning (EF), to determine the rest-activity rhythm, emotional wellbeing, i.e. quality of life (QOL) and the level of depressive symptoms in patients with early-onset dementia (EOD), and 2) to investigate the potential effects of different exercise interventions on cognitive functioning, i.e. in particular EF, (instrumental) activities of daily living ((i)ADL), and QOL in patients with EOD. The main outcomes are summarized below.

Summary

CROSS-SECTIONAL STUDIES IN PATIENTS WITH EARLY-ONSET DEMENTIA

In **chapter 2**, the relationship between the level of physical activity and measures of EF was investigated. Physical activity was measured using a pedometer and a self-report questionnaire. A statistical trend for a positive relationship was found between category fluency, a measure of semantic memory and set-shifting, and mean steps per day (pedometer). No other relationships between measures of EF and measures of physical activity were found. The outcomes indicate an inconsistent relationship between EF and the level of physical activity in EOD.

In **chapter 3**, we studied parameters of the rest-activity rhythm, one of the circadian rhythms, and sleep parameters in patients with EOD. Also, it was explored which demographic, clinical, and lifestyle factors contributed to disturbances in the rest-activity rhythm. The results showed a trend towards a higher "Intradaily Variability" in patients with EOD compared to cognitively intact adults of the same age, which means that the rest-activity rhythm of patients with EOD was more fragmented within 24-h. Patients with EOD also spent more time in bed and needed more time to fall asleep than controls. Disturbances in the rest-activity rhythm were associated with a lower level of physical activity, the use of antidepressants, the use of medication

for neurological disorders of the central nervous system, and with being male. The finding that the level of physical activity is related to disturbances in the rest-activity rhythm is of particular interest for these young patients, because they are better capable to perform physical activity then elderly persons, and hence can adopt an active lifestyle more easily, which might benefit the rest-activity rhythm.

Finally, in **chapter 4** we studied the level of QOL and depression in patients with EOD; whether QOL was lower and depressive symptoms were more frequently present in patients with EOD compared to cognitively intact adults of the same age; and which demographic, clinical, and lifestyle factors contributed to QOL and depressive symptoms. Patients with EOD reported an overall "good" QOL, while controls reported "very good" QOL. Twenty-one percent of the patients with EOD and eight percent of the controls were depressed. QOL was lower and depressive symptoms were more frequently present in the EOD group compared to the control group. More depressive symptoms were associated with a more fragmented rest-activity rhythm. More depressive symptoms were associated with a lower QOL. These findings give an indication of emotional wellbeing in patients with EOD.

Taken together, the outcomes of the cross-sectional studies indicate that 1) the relationship between measures of EF and physical activity is inconsistent; 2) the level of physical activity is related to disturbances in the rest-activity rhythm, which are slightly more pronounced in patients with EOD compared to cognitively intact controls of the same age; 3) emotional wellbeing is reasonably good in the current EOD population and more depressive symptoms are related with a more fragmented rest-activity rhythm. These findings shed some light on relations between clinical and lifestyle factors in EOD, which may be further investigated in future research endeavors.

AN EXERCISE TRIAL IN PATIENTS WITH EARLY-ONSET DEMENTIA

First, in **chapter 5**, a theoretical framework was developed to estimate the value of exercise interventions in early-onset Alzheimer's disease (EOAD). A literature search was conducted on key words related to early-onset dementia, exercise, imaging, neurobiological mechanisms and cognitive reserve. Since literature results only included studies concerning early-onset *Alzheimer's disease*, this review focused on EOAD specifically, instead of EOD in general. The results of the review showed that brain regions, such as frontal and parietal regions, and neurobiological processes, such as neurogenesis and synaptogenesis, involved in the positive effects of exercise, are affected in EOAD, which provides theoretical support for exercise interventions in EOAD.

In **chapter 6**, we proposed the study protocol of the intervention trial. We aimed to recruit 150 patients with EOD divided over three intervention arms. After completion of the baseline measurements, patients living within a 50 kilometer radius of one of the rehabilitation centers were randomly assigned to either an *aerobic exercise program in a rehabilitation center* or to a *flexibility and relaxation program in a rehabilitation center.* These programs were applied three times a week during 3 months and were supervised by a physical therapist. Participants living outside the 50 kilometer radius were included in a *daily physical activity program at home using pedometers.* This program used exercise counseling to coach the participants. For all participants, measurements took place at baseline (entry of the study), after three months (end of the exercise program), and after six months (follow-up). Primary outcomes were cognitive functioning, (i)ADL, and QOL. Secondary outcomes included a variety of physical, cognitive, and rest-activity rhythm measures.

Conducting the exercise trial proved to be more problematic than thought beforehand. In **chapter 7** the specific challenges faced and the lessons learned were discussed. The main challenges were: recruiting enough patients with EOD; logistics around the rehabilitation centers; and assessment

of tests for cognitive functions, in particular tests for EF. Recommendations for future research are the consideration of busy lifestyles of young patients, i.e. making intervention programs flexible to match these lifestyles, and offer the programs as close to home as possible. Finally, we recommend considering implementation of alternative measurements besides classical EF tests.

Taken together, we were not able to meet one of our main research aims, i.e. to investigate the effect of different exercise interventions on cognitive functioning, (i)ADL, and QOL in patients with EOD. In the general discussion we reflect on our study and give suggestions for care and research with patients with EOD and for future exercise intervention studies. We will focus on QOL in EOD, research in EOD in general, and physical activity research in EOD.

General discussion

QUALITY OF LIFE IN EARLY-ONSET DEMENTIA

Although more and more studies focus on EOD, patients with EOD are still underrepresented in research. It is however important to include patients with EOD, because studies that focus on EOD could contribute to the development of specific care facilities. At this moment patients with EOD have to ultimately rely on care facilities that are in most cases developed for elderly people with dementia. There are hardly any care facilities and interventions available that take into account the specific characteristics and needs of patients with EOD.[1] This is unfortunate, since patients with EOD are a distinct group with age-specific needs.[1–3] One of the targets of our project was to include patients with EOD with a mild to moderate stage of dementia, who showed decline in the level of physical activity. However, the present study population with EOD consisted of patients who were willing to participate in an exercise intervention. The participating EOD patients may have better health and may be more active than EOD patients who were not willing to participate.[4] In other words, we had a selected group of patients, limiting

the generalizability of our cross-sectional findings to the general EOD population. We found that the patients in this study were outspoken, undertaking, and critical. Many patients (and caregivers) had active lifestyles. Some patients still worked (on a therapeutic basis) or volunteered. Also, we experienced that patients wanted to enjoy their lives to the fullest by travelling or by spending time with their children. In these active patients with EOD, we found that QOL was good (**chapter 4**). QOL was better in patients with EOD with less depressive symptoms and depressive symptoms were fewer in patients who had less intradaily transitions between active and resting periods in the rest-activity period (**chapter 4**). This rest-activity rhythm parameter (Intradaily Variability), together with the stability of the rest-activity rhythm over days (Interdaily Stability), appeared to be related to physical activity (**chapter 3**). Hence, by increasing the everyday level of physical activity in patients with EOD you might influence the rest-activity rhythm, but indirectly also the level of depression and even QOL. Physical activity could be offered as part of day care facilities, for instance by organizing regular supervised walks. When walking is performed outside, the daylight might benefit the rest-activity rhythm as well, through increased melatonin secretion.[5] We further believe that for our young and active population it would be beneficial if care facilities were flexible, for instance available outside working hours, and specialized in EOD. Other Dutch researchers and health care professionals have suggested similar care.[6,7] For instance, the Dutch EOD steering committee pleads for dedicated care, meaning that diagnostic and care services should be integrated, in order to stimulate specialized services.[7]

RESEARCH IN EARLY-ONSET DEMENTIA IN GENERAL

In research, selecting appropriate outcome measures that are both sensitive and feasible is very important. In this thesis a wide range of outcome measures was administered: cognitive tests, among which EF tests; self-report questionnaires about (i)ADL, QOL, and depressive symptoms; and measurements with technical devices, such as pedometers and actiwatches.

We experienced that some outcome measures were better feasible in our study participants with EOD than others. Concerning measures of physical activity, we had positive experiences with two devices that can be worn by the patient: a pedometer and an actiwatch. Both devices were tolerated well. It was relatively easy for the caregivers to assist the patients when needed. The pedometer gave us valuable information about the level of physical activity in daily life. Most physical activity studies use subjective measures to assess the level of physical activity, such as self-report questionnaires.[8] Questionnaires on physical activity may be subject to limited reliability and validity.[9] Measurements with devices that can be worn by the patient provide objective information about the level of everyday physical activity.

Less feasible were measures of EF, for example the Trail Making Test B, on which we had substantial missing values. These missing data were caused by not comprehending test instructions, or by the inability to perform the required task, and made us decide to leave certain tests out of the analyses (**chapter 2**), and to not analyse the intervention data (**chapter 7**). In **chapter 2** we suggested that classical EF tasks might be less suitable for evaluation of patients with EOD in research. A considerable number of patients with EOD have pronounced EF disorders, which are present already in mild stages of dementia.[10] In clinical practice, classical EF tasks are very valuable, because observations of why a person was not capable to perform the test are informative.[11] These qualitative observations are difficult to incorporate in research. In addition to classical EF tasks, alternative tasks could be considered that also appeal to frontal lobe function. One option might be tasks measuring aspects of Theory of Mind (TOM). TOM is the ability to attribute beliefs, intentions, desires, and feelings to oneself and to others, and is crucial for social interaction.[12] TOM tasks rely on frontal lobe functioning.[13] Several TOM tasks, such as First and Second Order False Beliefs Written Passages,[14] the Faux-Pas Test,[15] the Mind in the Eyes Test,[16] and the Cartoon's Task,[17] are related to EF performance,[18] but the exact nature of this relationship is unknown.[18] It is hypothesized that the relationship might be either the result of a neuroanatomical overlap between the two constructs,[19] or of a

functional dependence,[19] meaning that you would need EF to perform TOM tasks, or the other way around. An advantage of adding TOM tasks might be that test instructions of TOM tasks are less complex than instructions of classical EF tasks, which might make TOM tasks more feasible. For example, in the Cartoon's Task the patient is presented with several jokes (cartoons) and the patient is simply asked to explain the jokes.[17] Also, the cartoons give the task a rather playful character, which may limit frustration during the examination. A recent study showed impaired performance on TOM tasks in different dementia suptypes.[20] In future studies it could be explored whether TOM tasks are a feasible and sensitive measure in studies in patients with EOD.

PHYSICAL ACTIVITY RESEARCH IN EARLY-ONSET DEMENTIA

TYPE OF EXERCISE

In this thesis we investigated three different physical activity interventions. The goal was mainly to bring patients from an inactive state back to a normal level of physical activity. In other words, the goal was not to perform excessive amounts of exercise, but to combat inactivity. A healthy amount of physical activity for a person of middle age includes 150 minutes of moderate to vigorous physical activity throughout the week.[21] Researchers use a wide variety of interventions to study the effect of exercise on cognition.[22] There is ongoing debate about what type of training is most beneficial for cognition. Historically, intervention trials studying the effects of exercise on cognitive functioning, examine the effect of aerobic training.[23] Aerobic training increases cardiovascular fitness, and includes endurance activities such as cycling, running, or swimming.[21] In trials, aerobic training is either compared with non-endurance training, such as stretching exercises,[24] or with a passive control group, such as care as usual.[25] Stretching exercises as control condition has the advantage that when using a similar design, the study focuses more on the actual difference in intensity of physical activity. However, low intense physical exercise, such as stretching exercises, may also have an impact on cognitive functioning, as was recently shown.[26,27]

Other types of physical activity, such as resistance training and coordination training were also found to benefit cognitive functioning.[28,29] It might be that different types of exercise influence different cognitive functions, through the stimulation of different neuroanatomical substrates.[30] Which type of training, i.e. aerobic, strength, or coordination training, is most effective in patients with EOD has yet to be studied.

COMBINING TRAINING PARADIGMS

Most studies focus on one type of physical activity, but a combination of aerobic and strength training may have a synergistic effect on cognition;[23] a suggestion supported by findings from studies in sedentary older adults and in adults who suffered a stroke.[23,31] Another combination of training paradigms that might be fruitful, is the combination of aerobic training and cognitive training. Animal studies indicate that the combination of aerobic training and cognitive enrichment might especially benefit cognition.[32] Indeed, in cognitively intact older adults, combined aerobic training and cognitive training of memory posed additional effects on memory functioning compared to either training separately.[33] It has been suggested that the mechanism behind the added effect of a physical-cognition training might be that exercise prepares the brain for the cognitive stimulation, leading to larger effects of the cognitive stimulation.[34] Whether this combined training method would also be effective and feasible in populations with EOD is an interesting target for future research endeavours.

INTENSITY, FREQUENCY, AND DURATION OF EXERCISE

When performing an intervention trial the intensity, frequency, and duration of the intervention program have to be considered. Concerning studies with patients with dementia, the designs of exercise trials are heterogeneous.[22] In the present trial the intervention programs lasted for 3 months with a frequency of 3 times a week, which is considered the minimal amount of exercise to increase cardiorespiratory fitness.[35] When designing a trial, factors that capture the effect and factors that make the study feasible need to be in balance. It is best when exercise is sustained for a longer time,[35] however very lengthy trials are more expensive in terms of man hours, and might be subject to higher loss to follow-up. Heterogeneity in study designs may

contribute to the mixed results that are found in exercise trials in persons with dementia.[22] Creating uniformity in trial designs is necessary in order to be able to compare results from multiple trials and hence draw more general conclusions. More randomized controlled trials are needed to provide clarity about what type of training, which duration, and which intensity is most beneficial and still feasible in patients with dementia in general, and in patients with EOD specifically.

EXERCISE COUNSELING AT HOME

Our third intervention program, the program at home making use of pedometers, was aimed to increase everyday physical activity. This program was based on the COACH method,[36] applying an exercise counseling program in combination with a pedometer as a motivational and feedback tool.[37] An advantage of this program was that it could be implemented in participants' daily life. The home visits by coaches were experienced as pleasant both by patients and caregivers. The exercise counseling was based on motivational interviewing techniques.[38] The coaches experienced that the motivational interviewing techniques were challenging to perform with EOD patients. Several patients were not fully able to give to-the-point answers to the questions, meaning that they easily deviated from the subject. The caregivers were allowed to support the patients during the interviews, however a certain level of comprehension and insight of the patient was required in order to discuss changing behaviours. Nevertheless, the pedometer was tolerated well by the patients with EOD. Several patients kept using the pedometer as a feedback tool for the daily step count after the intervention was finished. This experience leads to our suggestion to develop a less cognitively challenging coaching program aimed at the use of the pedometer, in order to stimulate physical activity in the EOD population.

MOTIVATION

For our intervention, we intended to include primarily physically inactive patients with EOD. A physically inactive lifestyle has negative outcomes on cognition.[39] Also, it is thought that particularly physically inactive persons might benefit from an increase in physical activity,[40] making especially the physically inactive patients interesting treatment targets. It turned out to

be very difficult to motivate physically inactive patients with EOD to participate. Physically inactive lifestyles in EOD may be caused by disturbances in EF and apathy.[41,42] It is known that apathy in patients with dementia coincides with a lack of motivation.[41] From a research perspective, the question arises how motivation in persons with EOD can be enhanced. The Self-Determination Theory (SDT),[43,44] describes three basic psychological needs that are closely related to the development of motivation.[15,45,46] These needs could help to understand the lack of motivation in EOD patients, and could also help to develop strategies to enhance motivation to participate in exercise interventions. First, when we apply the basic psychological needs to our study, according to the need for competence some patients with EOD may not have felt competent enough to participate in an exercise trial,[45] meaning that they may felt that they were not physically fit or skilled enough.[47] A strategy to attenuate this may be providing explanations (repeatedly) about what the intervention contains. Second, according to the need for autonomy,[15] patients with EOD may have chosen not to participate because they did not feel they had enough freedom of choice. In view of this need, randomization might be troublesome, because it limits the freedom of choice in what activity the patient is going to perform. To enhance feelings of volition, the exercise program could be made flexible, meaning that patients could fit the program into their daily life, in comparison to fixed training hours. Finally, the need for relatedness suggests that our participants may not have felt related enough to the person initiating the exercise.[46] Perhaps, if the training (period) is preceded by a social activity with the researcher or physical therapist, such as drinking coffee or a face-to-face meeting in which the intervention is explained, feelings of relatedness may be increased and patients may be more inclined to participate. In future exercise trials, the Psychological Need Satisfaction in Exercise (PNSE) scale could be implemented, in order to assess the satisfaction of the three basic psychological needs during the trial.[48] However, before the PNSE tool can be used in studies with patients with EOD, the tool has to be validated in this population.

Conclusion

To conclude, in this project we had difficulties with performing an exercise trial with patients with EOD. Nonetheless, by sharing our reflection on the present research we illuminate possibilities and recommendations for future exercise studies in patients with EOD. Since no cure for dementia is available in the foreseeable future, non-pharmacological interventions are important to consider, for they can contribute to the development of suitable and effective care facilities.

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