Physical and Cognitive Exercise for Patients with Dementia

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List of Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
BDNF	Brain-derived neurotrophic factor
CS	Cognitive stimulation
EEG	Electroencephalography
MCI	Mild cognitive impairment
QoL	Quality of life
RCT	Randomized controlled trial
rs-fMRI	Resting state functional MRI

Introduction

Physical and cognitive exercise (in this chapter, cognitive exercise refers to cognitive stimulation and cognitive training) for patients with dementia encompass a somewhat heterogeneous group of interventions which vary greatly with regard to design, implementation, targeted population, and efficacy. The term non-pharmacological treatments may at times be used to encompass these types of specific interventions. Although it is difficult to define what is meant by non-pharmacological treatment, it is implicit that such treatments do not include stand-alone pharmacological treatment, and usually also do not include invasive

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procedures such as surgery. They are rarely alternatives to pharmacological treatment but are often adjuvants to it, e.g. by interacting with pharmacological treatments, mitigating side-effects or improving compliance. This is also true for physical and cognitive exercise.

This chapter will give an overview of the evidence that exists regarding possible effects of physical and cognitive exercise in dementia.

Methodological Considerations

Physical and cognitive exercise may be considered complex interventions. Complex interventions have several interacting components (e.g., exercise may have an effect on the cardiorespiratory system, coordination/balance and may also have an effect by the social interaction) and may include behaviors by those who deliver and receive the intervention which have a high degree of difficulty. Indeed, some interventions may not be immediately implementable in clinical practice in a particular center or nursing home but may require staff training or training of caregivers or the need for adaptation of the usual clinical routine in order to accommodate the treatment [1, 2]. Moreover, some degree of flexibility may be necessary in order to ensure the ability of the treatment to be implemented in variable settings.

This also raises the issue of how such interventions can be evaluated for efficacy as the methodology used in randomized controlled trials (RCTs) of pharmacological treatments may be inappropriate or not transferable to the evaluation of exercise interventions. Physical and cognitive exercise interventions, together with other non-pharmacological treatments should ideally be evidence-based and thus despite obstacles to the evaluation, rigor in the assessment must be maintained and insisted upon. This is also important from a patient safety point of view, since although the interventions are generally considered safe and with relatively few adverse effects, such cannot be ruled out before evaluation. Moreover, implementing non-pharmacological treatments will often be associated with resource-consumption which will prohibit other activities, and it is obviously counter-productive to introduce treatments for which there is evidence of no effect.

For the aforementioned reasons, the UK Medical Research Counsel has developed a methodological framework for the evaluation of complex interventions, such as physical and cognitive exercise, from hypothesis generation to implementation, and also suggests various study designs and other methodologies (e.g., consideration of alternative endpoints or study designs) adjusted to the evaluation of complex interventions [3]. In this vein it should also be kept in mind for clinicians and others evaluating the literature on exercise and other non-pharmacological treatments in dementia that the usual gold standard for the evaluation of pharmacological treatments, i.e. a double-blinded RCT, will be unattainable for interventions such as physical exercise. Indeed, it may be an inappropriate methodology for evaluating a large proportion of non-pharmacological interventions.

Physical Exercise

For many years, exercise has received increasing attention as an important factor in maintaining health and wellbeing for humans of all ages. From an evolutionary point of view, being physically active has always been a stable of human existence as the vast majority of our time as a species have been spent as hunter-gatherers employing a strategy which involved traveling large distances by foot at a relatively high speed [4]. It is, therefore, not surprising that physical activity may impact on many organs and organ systems, and that physical inactivity may have detrimental impact on health. In other words, physical activity is a prerequisite for good health even in old age and in the presence of chronic diseases. In this vein, and specifically related to the brain it is interesting to note that the evolution of Homo Sapiens from apes coincided with a remodeling and growth of skeletal muscle and the brain in parallel further highlighting a linkage between muscle and brain [4]. This goes beyond the mere control of muscle which is subserved by a number of central and peripheral nervous system parts. However, this evolutionary perspective is more indicative of the role of physical exercise in the prevention of the occurrence of disease, and less so to the treatment of an acquired diseases such as dementia. Nevertheless, an interest in this aspect with regard to dementia and mild cognitive impairment (MCI) has become an increasing focal point in research within recent years as evidence has accumulated of an effect of physical exercise on the brain and symptoms of dementia. Physical activity has been defined according to the World Health Organization stating that "physical activity as any bodily movement produced by skeletal muscles that requires energy expenditure. Physical activity refers to all movement including during leisure time, for transport to get to and from places, or as part of a person's work" [5], whereas physical exercise is physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body. Thus, some persons may have a very physically active life but enjoy little physical exercise, whereas for others, the physical activity in their lives consists of exercise. For patients with dementia, having a physically active life may be difficult due to impairments prohibiting engagement in normal activities such as gardening and housekeeping or walking, and physical exercise may not be accessible to patients with dementia. For example, for persons with dementia exercise may need to be specifically tailored, or they may reside in assisted living facilities where physical exercise may not be made available.

Exercise and the Brain: Effects and Underlying Mechanisms

A large number of studies using different methods of investigation such as electroencephalography (EEG), brain scans, cognitive testing, biochemical analysis, and genetic and epigenetic analysis have studied the effects of exercise on the brain and possible underlying mechanisms (Fig. 13.1).

It has become evident from a number of studies using structural MR scans of the brain that being physically active affects the structural properties of the brain.

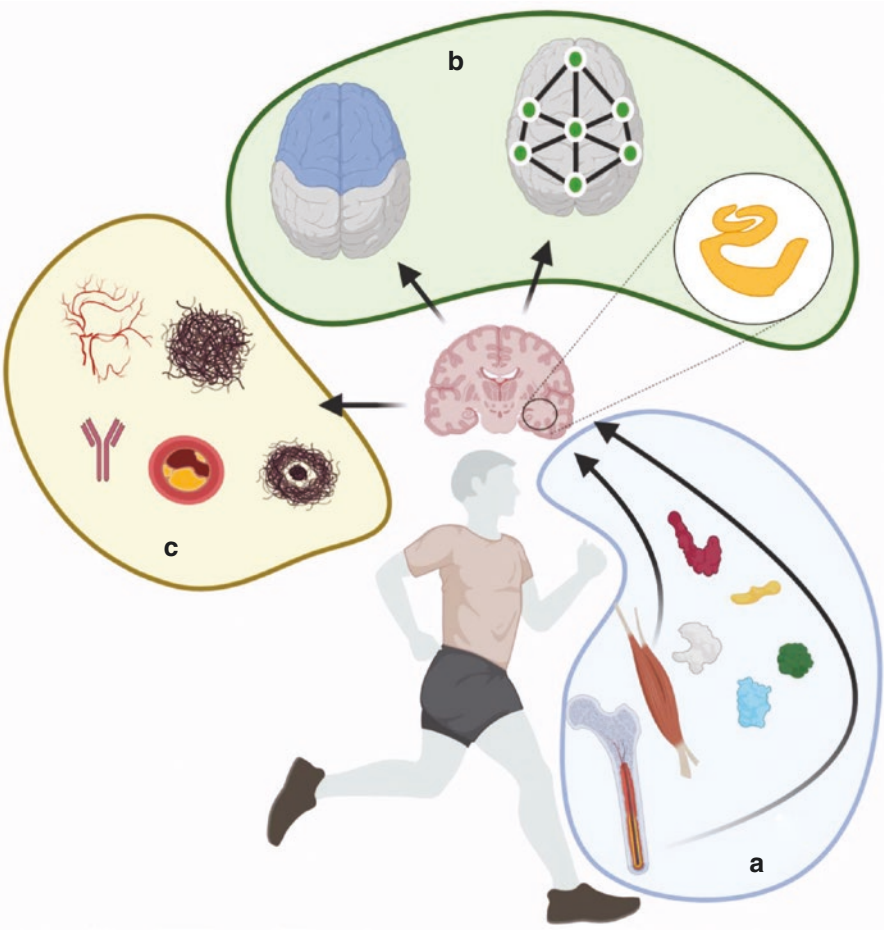

Fig. 13.1 Role of exerkines in the effects of exercise on the brain. A number of exerkines (**a**) such as brain-derived neurotrophic factor (BDNF), irisin, cathepsin B, interleukine-6, and other molecules from muscle and osteocalcin from bone may be released into the blood stream and enter the brain (brain–muscle cross-talk). Evidence from animal and human studies suggest a possible effect of exercise on a number of brain regions (**b**) such as the hippocampus, frontal cortical areas, and brain networks. Other effects may be mediated through an effect on beta-amyloid, vascular pathology, angiogenesis, neurogenesis, and anti-inflammatory effects

Evidence comes from observational studies offering indirect evidence, but data from interventional studies also support this. A relatively large focus has been on the hippocampus with earlier studies finding the hippocampus to be especially responsive to exercise in terms of volume change [6–8]. Subsequent studies in humans have however, been less convincing, and a relatively recent meta-analysis pooling 14 studies failed to find convincing evidence for an effect [9]. Intriguingly, the hippocampus is one of the few areas in the brain where adult neurogenesis has been shown to occur in humans [10], and it has been speculated that an effect may

be mediated through stimulation of neurogenesis [11]. Animal studies support the notion that exercise preserves adult neurogenesis in the dentate gyrus in Alzheimer's disease (AD) mice, and thus may also hint at a role in patients with AD regarding exercise [12]. Studies examining hippocampal subfields have not been able to find that exercise specifically stimulates volume changes in the dentate gyrus [13, 14], where adult neurogenesis takes place [10]. Maass et al. investigated whether vascular plasticity in the hippocampus was affected by a 3-month aerobic exercise program in sedentary older adults (60–77 years) and found that perfusion increased in the oldest participants and that change was correlated with improvements in hippocampus-dependent cognitive tasks [15]. This thus indicates that an effect of exercise on the hippocampus may be mediated by other mechanisms than volumetric changes. Long-term potentiation, which is believed to be the cellular basis of memory formation, and alterations in neurocircuitry may be other changes induced in the hippocampus by exercise which may not lead to volume changes [16], but may nevertheless improve hippocampal function such as memory.

Other areas of the brain are also possibly affected by exercise including frontal areas and the white matter. Regarding the white matter, fractional anisotropy, a measure of microstructural integrity derived from diffusion-weighted MRI, in the corpus callosum was cross-sectionally correlated with peak oxygen uptake in one study [17], but findings in the corpus callosum are not consistent across studies [18]. In a large observational study, measures of cardiorespiratory fitness and whole brain white matter integrity 5 years after assessment were found to be associated [19], and in another large study, self-reported physical activity was associated with preserved integrity of frontal lobe tracts including the genu of corpus callosum, uncinate fasciculus, external capsule, and anterior limb of the internal capsule [20]. Lastly, and in a smaller study, amount of physical activity was associated with higher integrity of white matter of the left fornix [21]. Moving to intervention studies, whole brain white matter atrophy in older women was attenuated following a 2 year resistance exercise program [22], and in another study, 1 year of weekly aerobic exercise also improved white matter microstructure in frontal areas [23]. As interventions of shorter duration did not lead to changes in the white matter [24, 25], it may be speculated that longer interventions may be needed to affect white matter. Since the primary function of white matter tracts is as structural connections between different cortical and subcortical areas, assessing the effects of exercise on neural networks may be an indirect way to assess white matter function. Two commonly applied methods to assess networks are resting state functional MRI (rs-fMRI) and resting state EEG. Gramkow et al. reviewed the literature regarding the effects of acute exercise interventions on resting state EEG and found that in general, studies were small, with varying methodologies and low methodological quality [26]. It was not possible to arrive at any conclusion regarding effects on networks, and an effect of exercise on the delta band was the most consistent finding [26]. Regarding rs-fMRI, Dorsman et al. longitudinally investigated 212 healthy elderly persons and found that inter-network inter-subject synchronicity in subcortical and frontal-subcortical networks increased with amount of self-reported physical activity over time. There was no association between other networks and physical activity,

including the default-mode network [27]. A small number of intervention studies have also investigated the effects of exercise on network connectivity and other metrics, and effects have been reported for the sensori-motor network [28], default-mode network [29, 30], and fronto-parietal network [29].

A comprehensive review of the literature regarding exercise and cognition in older adults is not possible in this chapter, but the evidence has recently been reviewed in a systematic review [31] and a meta-analysis [32]. Especially executive functions are improved by exercise, but also attention and processing speed [33] are affected. These cognitive functions are primarily reliant on frontal brain areas as well as more distributed brain networks, and thus in line with findings from MRI studies. This further highlights the notion that these parts of the brain are amenable to exercise. Also yoga [34] and Tai-Chi [35] seem to improve attention and processing speed. Indeed both aerobic, stretching and Tai-Chi are effective [32]. Chen et al. in their meta-analysis [32] found a possible dose-response effect for both frequency, intensity, duration and session duration. Whether memory is affected by exercise is less certain [36], but cannot be ruled out [37].

Despite the evidence suggesting a positive effect of exercise on brain structure and function, it remains largely unknown exactly what underlying mechanisms couple exercise and the brain. One intriguing possibility is that signaling molecules from peripheral tissues outside the brain such as muscle and bone are released into the blood stream and induce the changes. Skeletal muscle is metabolically very active during exercise, but also bone is activated by exercise, and both release molecules with autocrine, paracrine, and endocrine functions [38]. For muscle, these substances have been termed myokines, or, to reflect their relationship with exercise, exerkines [39] (Fig. 13.1). These include brain-derived neurotrophic factor (BDNF), irisin, cathepsin B, interleukine-6, and other molecules. BDNF has been most extensively investigated regarding an effect on the brain [39–43]. For bone and brain interaction, osteocalcin has been investigated [38, 44] and other candidates have been reviewed previously [38, 45]. Animal and cellular studies have shown that BDNF is associated with hippocampal function and is actively secreted [46]. In humans, a polymorphism in the gene coding for BDNF which leads to either a valine or methionine amino acid in BDNF has been shown to confer an increased risk of AD [47], and to modulate the protective effects of exercise on incident dementia [48] and interacts with the relationship between physical activity and hippocampal and temporal lobe volume [49]. Interestingly, in one study using a transgenic mouse model transfected with the methionine polymorphism, activation-induced secretion was reduced indicating that levels of BDNF protein have an important role [46]. A number of animal studies have further demonstrated that production and secretion of BDNF is induced by exercise. In humans, an acute bout of exercise in patients with depression increased serum BDNF [50], but a meta-analysis of chronic interventions in the same patient group did not find a similar increase [51]. This indicates that there may be a transient and immediate increase of BDNF following exercise but that the more tonic secretion is not affected by exercise. This may hint at two fundamentally different effects of exercise on the

brain, i.e. an acute effect possibly mediated through exerkines/myokines and a chronic effect partly mediated by other mechanisms (e.g., vascular, anti-inflammatory), but this remains speculative. BDNF has been coupled to a number of effects in the brain most principally neurogenesis [52], but also beta-amyloid production [53] and hippocampal dendritic spine density [54], and the exact linkage between exercise, BDNF, and the brain remains elusive. The evidence for a link between other myokines/exerkines and the brain remains less well examined.

Effects of Exercise in MCI and Dementia

The interest in exercise as a possible adjunctive therapy in dementia and especially AD is to some degree motivated by two lines of evidence. Firstly, animal studies have shown that exercise may remove pathological aggregates of protein and may ameliorate other pathological changes in the brain, and thus that being physically active reduces the risk of dementia and AD through these mechanisms [55]. Secondly, in observational studies physical activity has been shown to reduce the risk of cognitive decline [56].

In animal models of AD, exercise seems to effectively reduce the pathological deposition of beta-amyloid, a protein which is believed to be a central player in AD pathophysiology. This may happen through increased clearance, promotion of the non-amyloidogenic pathway, and reduced production of beta-amyloid [57–60]. Moreover, exercise also modulates tau protein and hippocampal volume, two other pathological hallmarks of AD [61, 62]. However, evidence remains scarce regarding this effect in humans. In a study of 16 weeks of aerobic exercise compared to usual care in patients with AD, cortical beta-amyloid was not reduced [63]. This to date remains the only study in which the hypothesis has been tested, and the negative finding may be due to the short intervention warranting further studies. Data on this issue from observational studies is inconclusive and neither support nor negate that physical activity is associated with reduced beta-amyloid (reviewed in [64]). Two studies examined the effects of exercise on hippocampus in AD patients [65, 66] and were not able to show an effect. Similarly, observational studies have not been able to establish a connection between physical activity and hippocampal volume in AD patients [67, 68].

Several studies have found that exercise mitigates symptoms of dementia and AD dementia. Exercise has been found to both reduce behavioral and psychological symptoms of dementia, improve activities of daily living (ADL) and improve cognition, and not only in patients with AD (e.g., [69–72]). This clearly demonstrates the potential of exercise as a component in the treatment of dementia. As in elderly persons without cognitive impairment, exercise seems to affect executive functions more than memory, but also general cognition [73]. Moderate to high intensity exercise is feasible in AD patients [74] and there may be a dose-dependent effect [70], although relatively low-intensity exercise has also been reported to improve cognition [75]. The effect on ADL may be mediated through an effect on physical

function, but may also be mediated through an effect on executive function [76]. Moreover, this may be due to a differential effect on more difficult ADL, so-called instrumental ADL, which may be more reliant on cognitive functions, and thus be less affected by exercise [77].

Planning and Adapting Exercise to Patients with Cognitive Impairment and Dementia

One of the advantages of physical exercise as an intervention in patients with dementia is that it may be modified and adapted to fit different needs such as preferences and abilities of patients, and available equipment and physical surroundings. It may also be combined with other interventions. Both aerobic, strength exercise, flexibility and balance training may be beneficial for patients with dementia. Moreover, exercise may be carried out inside or outside, in groups or individually, at home, in care facilities or in gyms. Some patients may prefer fitness training, whereas others prefer soccer, badminton, swimming, or other sports.

Some patients in the MCI or mild dementia stage will be able to participate in exercise and sports on equal terms with patients without cognitive impairment. However, a large share of patients will be dependent on a degree of adaptation of the activities to accommodate impairments in cognition and physical disability in order to exercise.

A myriad of different forms of exercise are feasible and acceptable to patients with dementia, such as moderate-to-high intensity aerobic exercise [36, 78], Tai-Chi [79], telemedicine based exercise interventions [80], strength exercise [81], and walking programs [82], but it is important to be aware of possible barriers to participation. In a systematic review, the following groupings of barriers were found for patients with dementia in care homes: physical health and mental wellbeing related reasons (e.g., acute illness, anxiety, fear of injury and frailty, low levels of previous activity level), relationship dynamics (e.g., disagreement within the group, family miscommunication), and socioeconomic reasons (e.g., low staffing levels). Similarly, a number of facilitators were identified: bio-medical benefits and benefits related to physical ability (e.g., physiological benefits, wellbeing), feelings and emotions and confidence improvements (e.g., mastery of engagement, empowerment, self-worth, regaining control), therapist, staff, and group relationship dynamics (e.g., anticipating challenges, availability of staff, motivating nursing assistants), activity related (e.g., allowing space for gaming approach, flexible approach, tailoring its approach and its safeness) [83]. A piloting phase may be advisable also outside research settings [74] as this will help adjust the exercise program to the specific needs of individual patients and patient group.

Another relevant consideration is whether exercise should be group-based or individual. Group-based exercise has a social component, which may give additional benefit. Many patients will need some guidance and assistance, and group-based exercise will enable a single instructor to oversee more patients at once than is possible with individual training, which may thus be more cost effective.

Unsupervised exercise may be feasible in some patients [84] but may also be associated with lower adherence [85]. Group-based exercise will usually be conducted outside the home for community dwelling patients. This may function as a "break" for family caregivers living with the patient, but also necessitates transport to the place where the activity will be organized. Prevention of injuries will include proper warm-up, adequate training, supervision by trained personnel, adequate equipment and clothing, and adaptation of the exercises to participants' cognitive impairment [74]. In this regard it is also important to be mindful of the risk of weight-loss which is often unwanted in patients with dementia as the disease itself means that patients are at risk of unwanted weight-loss (e.g., due to loss of appetite and forgetfulness regarding meals) (Table 13.1).

It is not possible from the literature to establish a lower limit to the exercise intensity or frequency of exercise which may elicit a benefit for patients with dementia. In this regard it is important to emphasize that apart from an effect on specific symptoms of dementia such as cognitive impairment, patients with

Table 13.1 Consideration regarding delivery of exercise programs to patients with dementia

Before an exercise program
Intended target population
• Degree of cognitive impairment and specific cognitive impairment (e.g., language comprehension problems, visuospatial) • Other symptoms of dementia (e.g., aggression, agitation) • Comorbidities and medication (e.g., musculoskeletal problems, beta-blockers (limits pulse increase)) • Community dwelling or assisted living • Motivations and previous experience with exercise
Setting and organization
• Individualized or group-based, at home or in a gym or other facility • Supervision and qualifications of those supervising • Need for transportation
Type of exercise
• Aerobic, strength, stretching, balance • On exercise machines, team sports, outside, indoors
Identify facilitatory and barriers
• Economic, resources, lack of previous experience, lack of a caregiver • Motivational factors (e.g., social element, providing music for exercise, small competitive elements, defining individual goals)
Consider safety
• Provide information about proper shoes and clothing • Information about warming up • Designing a ramp-up period in the intervention
During an exercise program
Make room for adaptation on the individual basis Consider barriers and facilitatory factors that may become evident during the program Be mindful of injuries Be mindful of caregiver burden associated with the patient's participation
After an exercise program
Give advice on maintenance of exercise habits

dementia will of course also benefit in other areas typically associated with engagement in exercise such as improved physical function and decreased risk of cardiovascular disease. In one study, patients with mild dementia improved cardiorespiratory fitness following a moderate-to-high intensity aerobic exercise intervention of 1-h session 3 times weekly for 16 weeks [86]. In a subset of patients participating in more than 66.7% of the offered sessions, improvements in walking speed and timed-up-and-go (a mobility measure) were observed [86]. Interestingly, in the same study, only those participants engaging in most of the offered exercise sessions improved on the cognitive outcome measure [86]. Two messages may be gleaned from these observations: (1) as for persons without dementia, there is a dose-response regarding improvements of physical fitness such as cardiorespiratory, and that ideally, one should engage in exercise a minimum of 2 times weekly, (2) that improvements in cognition may only be evident in patients who exercise at a relatively high intensity and frequency. However, this assumes that a possible effect on cognition is mediated either through improvement in cardiorespiratory fitness or a process which improves parallel with cardiorespiratory fitness. This remains speculative and needs to be examined in further studies examining the underlying mechanisms linking exercise and the brain.

Conclusion

Physical exercise is undoubtedly a prerequisite for health and longevity in humans. In patients with dementia, there may be an additional effect, as studies have found an effect of exercise on cognitive function and other symptoms. Processing speed, mental speed, and executive function may be especially sensitive to an effect of exercise, but memory may also be improved. Underlying mechanisms remain undetermined, but effects on frontal brain regions are plausible, whereas data for an effect on the hippocampus is less convincing. The role of myokines remains to be investigated. Exercise is a very flexible intervention which is applicable to any stage of the disease including in the severe stages of a dementia disorder, but appropriate measures to facilitate and to limit barriers for persons with dementia to exercise must be taken.

Cognitive Stimulation and Training

Cognitive stimulation (CS), cognitive training, and cognitive rehabilitation (latter covered in Chap. 14) are sometimes used interchangeable in research literature and in writings on their practical implementation. This has led to some confusion, and at present there are no definitions which are uniformly accepted. Indeed, elements of the three practices also overlap. However, a number of distinct characteristics unique for each of the approaches may be stated which has some validity and function, in that they relate to different underlying theoretical, conceptual assumptions, core elements and target populations, and therefore may have utility. All three

Table 13.2 Cognitive stimulation, cognitive training, cognitive rehabilitation

	Intervention—description	Target population	Setting	Possible mechanism of action	Goal
Cognitive stimulation	General activities believed to stimulate cognition	MCI, mild, dementia, moderate dementia	Usually in groups	General stimulation of cognition	Prevent decline ("use it or loose it")
Cognitive training	Tasks designed to train cognitive functions	MCI, mild dementia (moderate dementia)	Group or individualized	Targets impairment in cognitive functions	Restoration of specific cognitive functions and subsequent improvement in functions
Cognitive rehabilitation	Training in real-word situations	MCI, mild dementia	Individualized	Development and training of compensatory/adaptive mechanisms	Performance and functioning

approaches share the characteristic that they are focused on improving cognitive functions or to abate deficits in functioning caused by cognitive impairment [87].

CS usually refers to activities in which participants take part in a variety of activities that are often group based and viewed as being able to stimulate cognitive engagement (e.g., discussions, lectures, games), whereas cognitive training involves exercises or tasks which are designed to target specific cognitive functions. Through incremental increases in difficulty, cognitive training aims to improve the individual's level of ability within the domain being targeted. Cognitive rehabilitation is the development of strategies which are aimed at helping the participant to achieve specific goals (e.g., being able to keep appointments, participating in specific activities) usually set out by the participant. Therefore, cognitive rehabilitation is directed at improving performance in everyday life in contrast to cognitive training where the focus is on specific cognitive functions which may in turn improve performance [88] (Table 13.2).

Cognitive Stimulation

CS has a long history within therapies aimed at patients with dementia [89]. The basic tenet behind CS is to view the brain as a muscle in the sense that you "use it or loose it" [90]. Initially, CS was devised as a group-based activity, but in recent years, efforts to develop individualized CS have been underway [91]. CS is designed to stimulate general cognition, i.e. not specific cognitive domains in isolation (e.g., memory), the argument for this approach being that cognitive functions are not used in isolation, and therefore stimulation needs to target several brain functions at once [89].

Different types of activities and content have been used in CS. The initial RCT on CS in dementia, for example, used images and tasks related to the images to stimulate discussion. In one example from the study participants were presented with the dotted outline of an umbrella, with participants being asked to connect the dots. Subsequently, they were asked to draw an umbrella from a different perspective as well as a closed umbrella. This was followed by discussions with the umbrella as a starting point (e.g., about rain/the weather, parts of France where it rained a lot, etc.). An improvement in general cognition and memory function (measured by the Mini Mental State Examination and AD Assessment Scale—Cognitive Subscale) was found following this 5-week intervention study [89]. Building on this promising finding as well as further including techniques from reality orientation, reminiscence therapy, and multisensory therapy, Spector et al. developed a 7-week, twice weekly 45 min session program (15 sessions in total) which was piloted [92]. This type of CS is specifically referred to as CS therapy, and may only be practiced by trained therapists (see also International Cognitive Stimulation Therapy Centre website). The program could be implemented in care homes, and had sessions on "Current affairs," "Number games," "Food," "Being creative," "Faces/scenes," "Word game," and others [93]. The program was tested in an RCT with 201 persons with dementia (mild to moderate range), and was found to improve general cognition and QoL [94]. There were no between-group effects on measures of depression, anxiety, communication, behavior, or global functioning. A number of subsequent studies have been carried out on the effects of CS, but the aforementioned studies remain one of the largest with other studies ranging from a few participants to around 70–100 participants [95].

Two fairly recent meta-analyses [95, 96] have examined the effects of CS on AD and dementia in general, and have arrived at somewhat different conclusions. Oltra-Cucarella et al. [96] were able to include 14 studies in their analysis, all relatively small studies ranging from 4 to 20 participants. They did not find a significant effect of CS on general cognitive function, memory, or ADL when pooling data from the included studies. An important caveat in the interpretation of this finding is that as well as small sample sizes, the authors of the meta-analysis reported that in general risk of bias was high for a number of the studies included. Thus, caution in ruling out an effect in AD based on these findings is warranted. Huntley et al. in their meta-analysis [95] were able to include a total of 33 studies including the relatively large study by Spector et al. [94] and other larger studies [97–99] given the fact that they looked at dementia and not subtypes. Significant effects of CS on the Mini Mental State Examination and AD Assessment Scale—Cognitive Subscale was found. It seems reasonable to assume that the different conclusions in the two meta-analyses are due to the number of studies and sizes of included studies rather than a differential effect in general dementia versus in AD. This is also supported by findings in a third meta-analysis looking at CS in combination with acetylcholinesterase inhibitor treatment versus acetylcholinesterase inhibitor treatment alone in patients with AD, in which the former showed superiority regarding both cognitive function and behavior [100].

Huntley et al. [95] also examined a number of other factors by meta-regression analysis. The analyses revealed that format (inpatient vs outpatient; group vs

individual), dose (length, intensity of intervention in hours per week), or participant characteristics (dementia severity) were not associated with differences in effects [95]. Moreover, results did on differ depending on whether active or passive control situations were used [95].

A small number of studies have also investigated the effect of CS in MCI patients. Gomez-Soria et al. [101] tested a 10-week CS program in 155 patients characterized as MCI patients. The group-based intervention included reality orientation (questions about date, time and place, using calendars, etc.), practical exercises targeted at specific cognitive domains paired with an explanation of the cognitive aspect that was going to be focused on in each session, and finally group-based corrections of the exercises. There were no significant between-group differences in cognition, ADL, anxiety, or depression. In a much smaller study in patients with MCI due to Parkinson's disease (n=20), 7 weeks of individual CS improved cognition and some items related to ADL. However, patients were younger (age under 40 was an inclusion criteria), and replication in a larger study is needed. Two other studies examined whether CS in combination with exercise was beneficial [102, 103] in MCI patients. In the largest of the two, 555 patients were randomized to either cognitive stimulation, physical exercise, a combination, or social group (control). The interventions were based on 33 activities from Chinese culture (the study was conducted in Hong Kong) which were divided into cognitively activating, physically strenuous, or primarily social. The intervention could be completed in an activity center or at home and lasted for 12 months. All three interventions were found to improve measures of verbal fluency, delayed recall, and general cognition measured on the ADAS-cog. Subgroup analysis revealed that combined CS and exercise was superior to the others in improving verbal fluency. There were no effects on ADL, depression, or general function.

A number of modified approaches of the initial program of CS (i.e., CS therapy) have also been suggested, and in some instances tested. One modification has been the development of the maintenance CS therapy program. Initial studies of CS therapy had indicated that 3 months following the intervention effect of the intervention were minimal or not present [104], and were not detectable after 10 months [105]. Therefore, a program was developed [106] where the 7-week program [92] was followed by a maintenance program with once weekly sessions over 16 weeks. New sessions were added such as "Art discussions" and "Household treasures." A subsequent pragmatic RCT which included 236 care-home residents with dementia was conducted. At the 6-month follow-up significant improvements in self-rated Quality of Life-AD compared with the control group (7 week CS, but no maintenance). At the 3-month follow-up the proxy-rated QoL by carers, and daily activities showed improvements. There were no significant effects on cognitive scores or behavioral symptoms [107]. Maintenance CS therapy did likewise not improve the health of family caregivers of patients with dementia undergoing the intervention [108].

Another modified approach is individual CS therapy. An individualized approach has a number of advantages over group-based ones. Patients may have preferences that are not compatible with group-based activities, may have difficulty in interacting with groups, an individualized approach may be more easily implemented at

home and may be more implementable in areas where resources are scarce [109]. Orrell et al. [91] found that individual CS therapy improved the quality of the caregiving relationship and caregivers' QoL, but found no effect on cognitive function or patient QoL. The intervention consisted of a manual, and sessions were done at home with a caregiver. Each session had a theme, beginning with warm-up sessions (orientation using aids, current events) and moving on to the main session which could use artifacts from the home and were based on a specific theme which changed from session to session. The intervention was generally well accepted by participants and their caregivers, but was found to be best suited for those with less need for intensive support with barriers to participation being life commitments [110]. A high degree of acceptability is in line with previous findings including across different cultural settings [102, 111]. Lastly, it is worth mentioning that CS may also be delivered via computer [112] or telemedicine [113, 114] in an effective manner.

In conclusion, CS seems effective in improving general cognitive function and improving QoL in patients with dementia in mild to moderate stage and may have beneficial effects on family caregiver health. The most solid evidence exists for CS therapy. For this reason, the therapy has been recommended in the World Alzheimer's Report 2014 for patients with dementia as well as by the National Institute for Health & Clinical Excellence guidelines (2006) in the UK for treating cognitive symptoms of dementia. CS may also be effective in MCI, but the evidence base is smaller. In general, CS is well accepted by patients and is flexible in that it may be carried out in groups or individual, in care homes or in residential homes. Guidelines for adaptation of CS in different cultural settings have been developed [115] as has guidance on staff training [116], although the impact of such training is uncertain [117]. Cost effectiveness analyses indicate that CS therapy is most cost effective for those living alone and with higher cognitive function [118].

Cognitive Training

Cognitive training, sometimes referred to as "brain training," "retraining," or "remediation," is a process which uses a program or series of tasks, usually of incremental difficulty, that are designed to train cognitive functions. Cognitive functions usually refer to relatively specific cognitive domains such as memory, problem-solving, attention, or planning. The training targets one domain or domains which from a theoretical point of view are often used together. Cognitive training may be performed as a group activity or individually and may be performed as pen-and-paper exercises or computerized. As the intervention targets cognitive abilities, it has been suggested that the method may work better when combined with pharmacological treatment which improves cognitive function such as acetylcholine esterase inhibitors, but findings have not been convincing [119, 120].

A number of theoretical assumptions lie behind cognitive training. As previously mentioned, cognitive training is aimed at improving or maintaining underlying cognitive functions. In this connection "underlying" refers to those cognitive processes which are a prerequisite for the performance of ADL and therefore by extension,

that cognitive training results in improved functioning. This requires that cognitive functions are indeed trainable in the sense that they will either not worsen (i.e., remain stable) or even improve following training. The mechanism of neural plasticity is often referred to as a possible underlying biological mechanism, but evidence to support that cognitive training (or CS) is able to induce or promote neural plasticity, is scarce. Another assumption is that the effects of training will generalize, i.e. that the individual undergoing training not only improves on the specific task being trained (e.g., a memory task), but that this generalizes to other situations in which the individual engages memory. However, this last assumption has been difficult to prove [121]. Factors such as age and baseline cognitive performance have been shown to predict the effectiveness of the technique [122] and thus may explain why the effect is more pronounced in cognitively unimpaired individuals compared to cognitively impaired. Generalizability may be divided into near transfer (i.e., to positively affect cognitive functions closely related to or resembling that being trained) or far transfer (i.e., to positively affect cognitive functions no related to or resembling that being trained). The distinction between cognitive training and cognitive rehabilitation may at times be difficult, especially since cognitive training may be designed to draw on elements from a real-world setting (e.g., shopping).

It has been suggested to subdivide cognitive training into those programs which focus on training specific cognitive domains, and those which aim to train cognition optimizing strategies. One example of the latter is mental imagery. Mental imagery draws on the fact that images are more effectively encoded into memory than words (the picture superiority effect), and that spontaneous mental imagery may be elicited by words. Encoding of imagery versus words has been suggested to be subserved by different brain regions. Specifically, word encoding activates frontal and temporoparietal regions, whereas mental imagery activates visual areas [123], and thus may be less reliant on areas affected in, e.g. AD. However, while this strategy is effective in improving memory in elderly persons [124], this does not seem to apply to patients with AD [125]. Other cognitive training methods which have been tested in patients with AD include Trial and error, where the individual tries to guess the target which is to be recalled, and will receive fee-back on wrong guesses; Errorless learning, which involves reduction of the element of guessing by providing clues prior to performing the target task and Modeling with spaced retrieval, where the individual is asked to remember a sequence of steps in a task and after a delay reproduce the sequence. This may include both physical tasks and no-physical tasks. In a direct comparison of all three methods in mild to moderate AD, all three were found to be equally effective with regard to improving the ability to perform an instrumental ADL [126]. However, due to a lack of a control situation, and since generalizability was not tested, it is difficult to evaluate the effectiveness of the methods. A number of methods concerned with non-memory cognitive domains, including attention, written and spoken language, reasoning, concentration, praxis, and gnosis have also been tested in dementia populations [127–129].

In a recent Cochran review, Bahar-Fuchs et al. reviewed and meta-analyzed intervention studies of cognitive training in dementia [130]. An operational definition of cognitive training in the review was that the training had to target one or

more cognitive processes rather than a skill, and that the intervention was specifically designed to deliver the training. Further, the intervention could combine other components than strictly cognitive training. A total of 33 studies were included, with number of participants per study ranging from 12 to 653. The included studies varied greatly with regard to dosing such as length (from 2 weeks to 104 weeks), number of sessions (from, e.g., weekly sessions to more than one session per day), and duration of sessions (e.g., from 30 min to 1.5 h). Most studies included patients with mild to moderate dementia, with the intervention being delivered by either trained staff or caregivers. Pooled results showed an effect on global cognitive function when compared to control, and the effect seemed to last at least 3–12 months. However, there was no effect when cognitive training was compared to an active control (in contrast to a passive control situation). Data also showed an effect on specific cognitive domains including attention, language, and executive function. However, apart from effects on delayed memory and verbal fluency, the quality of evidence was low to very low. With regard to verbal fluency, subgroup analysis revealed that the effect was only present if the intervention was delivered more than three times a week and for interventions which targeted multiple domains. For ADL, caregiver burden and depression, the intervention was not effective. A single study reported data on caregiver wellbeing and mood for which there was an effect [131].

To conclude, cognitive training has yet to be shown to be effective but may carry some benefit for patients with mild dementia in regard to improving cognitive functions. Cognitive training may consist of different types of tasks, but data suggests a threshold of more than 3 sessions per week to be effective and should target more than one cognitive domain. Effects may be seen immediately following treatment and may be effective for up to 12 months. Cognitive training may be combined with, e.g., acetylcholine esterase inhibitors, but there does not seem to be an additional effect of this.

Conclusion

Treatment and management of dementia symptoms includes the appropriate use of non-pharmacological interventions such as those presented in this chapter. The interventions are safe and flexible meaning that they may be applied in diverse settings and taking the individual persons' preferences and abilities into consideration. Some interventions require staff training and adaptation to the specific setting. When implementing physical and cognitive exercise, knowledge of efficacy as well as barriers and facilitatory factors is necessary. Despite the obstacle to a rigorous evaluation of the efficacy and safety of physical and cognitive exercise, a growing evidence base exists to inform the physician about its effectiveness.

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