Department of General Practice and Primary Health Care
and
Department of Psychology and Logopedics
Faculty of Medicine
University of Helsinki

EFFECTS OF COGNITIVE TRAINING ON COGNITION AND QUALITY OF LIFE IN OLDER ADULTS WITH DEMENTIA

Eeva-Liisa Kallio

ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine, University of Helsinki, for public examination
in the University Main Building, Auditorium XII, Unioninkatu 34,
on 29 March 2019 at 12 noon.

Helsinki 2019

Supervisors

Professor Kaisu Pitkälä, MD, PhD
University of Helsinki, Department of General Practice and Primary Health Care
Helsinki, Finland

Docent Marja Hietanen, PhD
University of Helsinki, Department of Psychology and Logopedics
Helsinki, Finland

Professor Laura Hokkanen, PhD
University of Helsinki, Department of Psychology and Logopedics
Helsinki, Finland

Reviewers

Docent Laura Viikari, MD, PhD
University of Turku, Department of Geriatrics
Turku, Finland

Professor Roy P. C. Kessels, PhD
Radboud University, Neuropsychology and Rehabilitation Psychology
Nijmegen, The Netherlands

Opponent

Docent Mira Karrasch, PhD
Åbo Akademi University, Department of Psychology
Turku, Finland

ISBN 978-951-51-4895-7 (paperback)
ISBN 978-951-51-4896-4 (PDF)

Unigrafia
Helsinki 2019

To my family

Contents

Abstract

Dementia is an age-related, progressive and chronic syndrome. It is characterized by cognitive decline from a person's prior performance level, neuropsychiatric symptoms, and severe inability to manage everyday activities. The most common cause of dementia is Alzheimer's disease (AD), followed by other usually late-life disease pathologies such as vascular dementia, Lewy body dementia, and mixed dementia. The limited efficacy of current pharmacological treatment has directed research increasingly to non-pharmacological therapies for dementia. Several studies have focused on the effects of cognitive training (CT) in dementia, but the findings so far are inconsistent and conflicting.

This study, comprising four sub-studies, had two main objectives. First, the aim was to systematically evaluate the current evidence on the effects of CT in dementia. The focus was on randomized controlled trials (RCTs) including participants with established dementia, and using restorative or compensatory CT programs. Second, the feasibility and effectiveness of a systematic CT program for patients with mild to moderate dementia was investigated. The effects of CT on participants' cognition, psychological well-being, and health-related quality of life (HRQoL) were explored in a Finnish Cognitive Intervention (FINCOG) trial, which is a rigorously conducted RCT in a real-world setting.

In a systematic review, 35 RCTs concerning the effects of CT on cognition, functional abilities, psychological well-being, and/or quality of life of patients with dementia were found (Study I). The methodological quality of the trials was predominantly low, most often due to low statistical power, poorly described randomization methods, and non-robust statistical methodology. Furthermore, CT interventions were remarkably heterogeneous, trial drop-outs were inadequately described, and intention-to-treat analysis and long-term follow-up infrequently used. Beneficial effects of CT were primarily reported on global cognition and training-specific functioning, however, the limitations in research methodology decrease the current grade of evidence.

The FINCOG study is an RCT (n = 147) concerning the effects of a systematic CT program of 12 weeks conducted in adult day-care centers twice a week for 45 minutes (Studies II–IV). The participants were older home-dwelling patients with mild to moderate dementia randomized in two arms: CT intervention (n = 76), and control groups (n = 71). Both groups participated in regular adult day care. Measures of cognition, psychological well-being, and HRQoL were assessed before the intervention, and three and nine months after pre-intervention assessment. All the assessors were blinded to group allocation throughout the data collection.

In Study II, regular CT was found to be feasible among patients with mild to moderate dementia. Compliance with the intervention was good, the attrition rate low at post-intervention assessment, and feedback after the program for the most part favorable. General subjective gain was achieved by 76% of the feedback responders.

Studies III and IV report the findings on the effectiveness of CT on cognition, psychological well-being, and HRQoL. Systematic CT did not improve or stabilize global cognition in older persons with dementia (Study III). Both the intervention and control

groups declined in their global cognitive functioning according to ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale) over nine months, and the groups did not differ in their changes (p for group = 0.53, time < 0.001, group × time interaction = 0.43, adjusted for age and sex). Similarly, secondary cognitive outcomes concerning executive function, attention, working memory, episodic memory and reasoning indicated no effect of training (Study IV). Moreover, the participants did not benefit from CT either in terms of their HRQoL (Study III), or psychological well-being (Study IV).

To conclude, the available literature provides evidence of some beneficial effects of CT on global cognition, training-specific tasks, and occasionally on mood, in persons with dementia, but the quality of evidence is low. In the present RCT with rigorous design, conduct, and analyses, a 12-week systematic CT program for 90 minutes per week in small groups was found feasible, but CT did not improve or stabilize cognitive functioning, HRQoL, or psychological well-being of home-dwelling patients with mild to moderate dementia. Therefore, the findings of the FINCOG trial do not support the effectiveness of CT among older patients with established dementia.

Tiivistelmä

Dementia on ikään liittyvä, krooninen ja etenevä oireyhtymä. Sille on ominaista sairastuneen kognitiivisen ja päivittäisen toimintakyvyn huomattava heikentyminen toiminnan aiemmasta tasosta, sekä käyttäytymisen ja tunnesäätelyn muutokset. Tavallisin dementiaan johtava sairaus on Alzheimerin tauti, ja muita myöhemmällä iällä yleisiä syitä aivoverenkiertosairauden aiheuttama muistisairaus, Lewyn kappale -tauti ja sekamuotoinen muistisairaus. Koska saatavilla olevan lääkehoidon mahdollisuudet vaikuttaa muistisairauden kulkuun ovat rajalliset, on tutkijoiden mielenkiinto lääketutkimuksen rinnalla suuntautunut monimuotoisiin ei-lääkkeellisiin hoitomuotoihin. Kognitiivisen harjoittelun vaikuttavuutta muistisairailla henkilöillä on selvitetty useissa hoitotutkimuksissa, mutta tutkimusnäyttö on riittämätöntä.

Tämä väitöskirja sisältää neljä osatyötä, joissa selvitetään kognitiivisen harjoittelun vaikutuksia muistisairaiden henkilöiden toimintakykyyn ja elämänlaatuun. Ensinnäkin, tavoitteena oli arvioida systemaattisesti olemassa olevaa näyttöä kognitiivisen harjoittelun vaikuttavuudesta. Systemaattiseen katsaukseen hyväksyttyjen tutkimusten tuli olla satunnaistettuja kontrolloituja tutkimuksia, joissa raportoitiin kognitiivisen harjoittelun vaikutuksista muistipotilaiden kognitioon. Kognitiivisen harjoittelun tuli sisältää joko toiminnon palauttamiseen kohdennettuja tai muistioireiden kompensaatioon tähtääviä harjoituksia. Toisena tavoitteena oli tutkia säännöllisen kognitiivisen harjoittelun soveltuvuutta ja vaikuttavuutta muistipotilailla, joiden sairaus on lievässä tai keskivaikeassa vaiheessa. Harjoittelun vaikutuksia selvitettiin FINCOG (Finnish Cognitive Intervention) -tutkimuksessa, joka on huolellisesti suunniteltu satunnaistettu kontrolloitu tutkimus ja toteutettiin aidossa elinympäristössä osana ikääntyneiden päivätoimintaa.

Systemaattisen katsauksen (Osatutkimus I) kirjallisuushaku tuotti 35 katsauskriteerien mukaista tutkimusta. Vain neljä tutkimusta täytti tutkimusasetelmaltaan ja metodiikaltaan hyvätasoisen tutkimuksen laatukriteerit. Yleisiä metodisia puutteita olivat pieni otoskoko, epäselvä satunnaistamisen menettely sekä riittämättömät tilastoanalyysit. Tutkimuksen keskeyttäneitä osallistujia ei useinkaan kuvailtu tai huomioitu tuloksia analysoitaessa. Lisäksi tutkimuksissa käytetyt harjoitusmenetelmät vaihtelivat suuresti ja tulokset olivat vaikeasti vertailtavia. Harjoitusvaikutus näkyi muutoksina lähinnä yleisen kognitiivisen toiminnan tasossa ja harjoittelun kaltaisissa toiminnoissa, mutta tutkimustulokset arvioitiin valtaosin epäluotettaviksi metodisten heikkouksien ja näihin liittyvien mahdollisten virhelähteiden vuoksi.

FINCOG-tutkimuksessa (Osatutkimukset II-IV) selvitettiin satunnaistetun kontrolloiden asetelman avulla 12 viikkoa kestävän kognitiivisen harjoittelun (45 minuuttia kahdesti viikossa) vaikutuksia kotona asuvien iäkkäiden muistisairaiden kognitioon, psyykkiseen hyvinvointiin ja elämänlaatuun (n = 147). Suurin osa osallistujista sairasti Alzheimerin tautia sen lievässä tai keskivaikeassa vaiheessa. Tutkittavat satunnaistettiin kahteen ryhmään: kognitiivisen harjoittelun ryhmään (n = 76) ja verrokkiryhmään (n = 71), joka osallistui samaan päivätoimintaan kuin harjoitteluryhmä. Kognitiivisen harjoittelun vaikuttavuuden arvioimiseksi osallistujille tehtiin saman sisältöiset tutkimukset ennen harjoittelua, sekä

harjoittelun päätyttyä 3 kk ja 9 kk alkuarviosta. Kaikki tutkimukset tehtiin ryhmäjaolle sokkoutettuina.

Väitöstutkimuksen toisessa osatyössä (II) säännöllinen kognitiivinen harjoittelu todettiin muistipotilaille soveltuvaksi toimintamuodoksi. Hoitomyöntyvyys oli hyvä, keskeyttämismäärä matala ja osallistujien kognitiivisesta harjoittelusta antama palaute pääosin myönteistä. Kognitiivisen harjoittelun koki yleisesti hyödylliseksi 76% palautekyselyyn vastanneista.

Osatutkimukset III ja IV vertasivat kognitiivisen harjoittelun vaikutuksia muistisairaiden henkilöiden kognitioon, psyykkiseen hyvinvointiin ja terveyteen liittyvään elämänlaatuun. Systemaattinen 12 viikkoa kestänyt harjoittelu ei kohentanut tai vakiinnuttanut muistisairaiden kognitiivista suoriutumista (III). Sekä interventio- että kontrolliryhmässä ADAS-Cog -testillä arvioitu yleinen kognitiivisen toiminnan taso laski 9 kk seuranta-aikana merkitsevästi, eikä ryhmien välillä ollut eroa muutoksen määrässä (ryhmien välinen ero $p = 0.53$, muutos ryhmän sisällä $p < 0.001$, interaktio $p = 0.43$, ikä ja sukupuoli vakioituna). Vastaavasti kognitiivisen toiminnan eri osa-alueilla (toiminnan ohjaus, tarkkaavuus, työmuisti, episodinen muisti ja päättely) ei pystytty osoittamaan harjoitusvaikutusta 3 kk seurannassa (IV). Kognitiivisesta harjoittelusta ei myöskään havaittu olevan hyötyä osallistujien terveyteen liittyvään elämänlaatuun (III) tai psyykkiseen hyvinvointiin (IV).

Yhteenvetona todetaan, että aiempien tutkimusten mukaan kognitiivinen harjoittelu voi jossain määrin kohentaa tai ylläpitää harjoittelun ajan muistisairaiden yleistä kognitiivisen toiminnan tasoa, toimintakykyä harjoittelun kaltaisissa tehtävissä ja joskus myös mielialaa, mutta tutkimusnäyttö on ristiriitaista ja usein metodisesti vaatimatonta. Huolellisesti suunniteltu ja muistisairaiden aidossa elinympäristössä toteutettu satunnaistettu kontrolloitu FINCOG-tutkimus osoitti harjoittelun olevan toteuttamiskelpoista, mutta tutkimustulokset eivät tue kognitiivisen harjoittelun käyttöä muistisairauden lievässä tai keskivaikeassa vaiheessa. Säännöllinen 12 viikon harjoitusohjelma, joka sisälsi kognitiivisia harjoituksia 90 minuuttia viikossa pienissä ryhmissä, ei vaikuttanut kotona asuvien ja säännölliseen päivätoimintaan osallistuvien muistisairaiden henkilöiden kognitioon, terveyteen liittyvään elämänlaatuun tai psyykkiseen hyvinvointiin.

Abbreviations

AChEI	Acetylcholine Esterase Inhibitor
ACTIVE	Advanced Cognitive Training for Independent and Vital Elderly
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living
ADL	Activities of daily living
AGGIR	Grille d'autonomie Gérontologique Groupes Iso-Ressources
ANCOVA	Analysis of covariance
APA	American Psychiatric Association
BDI	Beck Depression Inventory
BNT	Boston Naming Test
CCT	Computerized cognitive training
CDR	Clinical Dementia Rating
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CG	Control group
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPM	Canadian Occupational Performance Measure
COWA	Controlled Oral Word Association
CPM	Raven's Colored Progressive Matrices
CPT	Continuous Performance Test
CRT	Cognitive remediation therapy
CT	Cognitive training
DAD	Disablement Assessment for dementia
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth edition
ES	Effect size
F	Female
FAB	Frontal Assessment Battery
FINALEX	Finnish Alzheimer Disease Exercise
FINCOG	Finnish Cognitive Intervention
FINGER	Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
fMRI	Functional Magnetic Resonance Imaging
FTLD	Frontotemporal lobar degeneration
F/U	Follow-up
G	Group
GDS	Geriatric Depression Scale
HRQoL	Health-related quality of life

I	Individual
IADL	Instrumental activities of daily living
ICD-10	International Classification of Diseases, Tenth edition
IG	Intervention group
ITT	Intention-to-treat
LBD	Lewy body dementias
MCI	Mild cognitive impairment
MDRS	Mattis Dementia Rating Scale
MMSE	Mini-Mental State Examination
MODA	Milan Overall Dementia Assessment
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke, and Association Internationale pour la Recherche et l'Enseignement en Neurosciences
NMDA	*N*-methyl D-aspartate
NPI	Neuropsychiatric Inventory
PI	Post-intervention
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PWB	Psychological Well-Being
QoL	Quality of life
QoL-AD	Quality of Life – Alzheimer's Disease
RAVL(T)	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
RCT	Randomized controlled trial
ROCF	Rey–Osterrieth Complex Figure
SD	Standard deviation
SRM	Standardized response mean
STAI	State Trait Anxiety Inventory
TAU	Treatment as usual
TMT	Trail-Making Test
VaD	Vascular dementia
VCI	Vascular cognitive impairment
VOSP	Visual Object and Space Perception
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth edition
WHO	World Health Organization
WMS-R	Wechsler Memory Scale – Revised
WMS-III	Wechsler Memory Scale, Third edition
15D	15-Dimensional measure of health-related quality of life

List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals:

I Kallio, E.-L., Öhman, H., Kautiainen, H., Hietanen, M., & Pitkälä, K. (2017). Cognitive Training Interventions for Patients with Alzheimer's Disease: A Systematic Review. Journal of Alzheimer's Disease, 56(4), 1349-1372.

II Kallio, E.-L., Öhman, H., Carlson, S., Kautiainen, H., Hietanen, M., & Pitkälä, K. H. (2017). Feasibility and baseline findings of a Finnish cognitive training (FINCOG) intervention in a randomised controlled trial among community-dwelling persons with dementia. European Geriatric Medicine, 8(3), 245-249.

III Kallio, E.-L., Öhman, H., Hietanen, M., Soini, H., Strandberg, T. E., Kautiainen, H., & Pitkälä, K. H. (2018). Effects of Cognitive Training on Cognition and Quality of Life of Older Persons with Dementia. Journal of the American Geriatrics Society, 66(4), 664-670.

IV Kallio E.-L., Hietanen M, Kautiainen H, Pitkälä K. H. Cognitive Training in Older Adults with Mild to Moderate Dementia: Evidence from a Randomized Controlled Trial (submitted).

1 Introduction

Dementia is a condition characterized by cognitive and behavioral decline from an individual's prior performance level, and severe inability to manage daily activities (McKhann et al., 2011). It is an age-related, usually progressive and chronic syndrome. While dementia can also affect younger people, onset of dementia after 65 years is typical, and the incidence increases rapidly with increasing age (Prince et al., 2015). Age is the strongest known risk factor of dementia (Hugo & Ganguli, 2014).

Dementia results from a variety of diseases and injuries that primarily or secondarily affect the brain, such as Alzheimer's disease (AD). A common feature in different forms of dementia is degeneration of the cells within the adult central nervous system. Neurodegeneration accounts for cognitive impairment, behavioral alteration, functional disability, and in an aging society, increasing caregiver burden and health-care costs.

The history of the term 'dementia' can be traced back to the eighteenth century and earlier (Boller & Forbes, 1998). The pioneering work of research groups led by Alois Alzheimer and Arnold Pick took place in the late nineteenth and early twentieth centuries, and since then a substantially improved understanding of dementia syndromes has emerged. Real progress in the treatment of dementia has occurred in the last 30 years. While currently available pharmacotherapies provide limited benefit, attention has been shifting to non-pharmacological approaches: diet and supplementation, exercise, social networks and cognitive intervention (Nelson & Tabet, 2015).

Deficits in cognition are the earliest symptoms in many neurodegenerative diseases, and research efforts have been focused on cognitive intervention with the aim of identifying effective therapies for preventing and slowing down the symptoms. Numerous studies, many of them randomized controlled trials (RCTs), have examined the effects of cognitive training (CT) and rehabilitation among dementia sufferers. However, heterogeneity and inconsistency in research and treatment methodology have complicated comparison of the treatments (Bahar-Fuchs, Clare & Woods, 2013; Huntley, Gould, Liu, Smith & Howard, 2015; Kurz, Leucht & Lautenschlager, 2011). To date, findings on the efficacy of CT in dementia are unclear.

This study has two main objectives. First, the aim is to systematically investigate the findings of previous RCTs concerning cognition-focused intervention, with a specific interest in CT in dementia. Second, the feasibility and effectiveness of a systematic CT program is explored in cases of mild to moderate dementia in regard to patients' cognition, psychological well-being, and health-related quality of life (HRQoL). The effects of CT are carefully explored in a Finnish Cognitive Intervention (FINCOG) trial, which is a rigorously conducted RCT in real-world setting.

2 Review of the literature

2.1 Dementia as a public-health challenge

Dementia is an umbrella term encompassing various neurodegenerative disorders, the most common being AD (Alzheimer's Association, 2018). Other common late-life disease pathologies are vascular dementia and Lewy body dementias, although in the oldest age groups mixed brain pathologies account for most dementia cases (Schneider, Arvanitakis, Bang & Bennet, 2007). Population aging has had a profound impact on the emergence of dementia, which has become a major target of health and social care, and an economic challenge worldwide (Prince et al., 2015).

2.1.1 Epidemiology of dementia

According to estimates from the World Alzheimer Report 2015, 46.8 million people worldwide have dementia, and this number is expected to increase to 75 million by 2030 and 131 million by 2050 (Prince et al., 2015). Although the age-specific incidence of dementia shows a decreasing trend in high-income countries (de Bruijn et al., 2015; Satizabal et al., 2016; Wu et al., 2017), dementia remains a major public-health challenge as a result of high worldwide prevalence and aging populations. The prevalence of dementia increases with age, and doubles every five years of age after the age of 65 (Hugo & Ganguli, 2014). In a Swedish population-based study 17.5% of individuals over 75 met the criteria for dementia (Qiu, von Strauss, Bäckman, Winblad & Fratiglioni, 2013), whereas in another European epidemiological study 25% of individuals over 80 met the criteria (Lucca et al., 2015).

Increasing age is not only a strong risk factor, but also the only risk factor of dementia identified after the eighth decade of life (Hugo & Ganguli, 2014). Annual age-specific incidence rates of dementia range from 0.1% at the age of 60–64 to 8.6% at the age of 95 (Gao, Hendrie, Hall & Hui, 1998). While prevalence is consistently higher among women, incidence is not; thus, the higher prevalence may largely be a consequence of longer life expectancy in women (Hugo & Ganguli, 2014).

In Finland, 100,000 persons are estimated to suffer from mild dementia and 93,000 persons from moderate or severe dementia, and the total number is expected to increase by 14,500 every year (Memory Disorders: Current Care Guidelines, 2017). According to population-based studies (Hänninen, Hallikainen, Tuomainen, Vanhanen & Soininen, 2002; Ritchie, 2004), there may currently be more than 200,000 persons in Finland living with mild cognitive impairment (MCI), which indicates an elevated risk of developing dementia in the near future (Petersen et al., 1999).

2.1.2 Symptoms of dementia

Dementia is characterized by progressive deterioration in personal abilities and capacity for independent living. It is a clinical syndrome, where cognitive impairment, loss of communicative abilities and skilled movements, and/or neuropsychiatric problems cause a prominent decline from previous levels of functioning, and reduce the ability to perform daily activities (McKhann et al., 2011). The neurocognitive and other problems parallel the underlying brain pathology over the course of the disease. As a consequence, different symptom patterns dominate the clinical picture of neurodegenerative diseases, especially in the earlier stages of the disease process.

The symptoms of a neurodegenerative disease can be categorized into three main groups: cognitive, neuropsychiatric, and neurological symptoms (Peña-Casanova, Sánchez-Benavides, de Sola, Manero-Borrás & Casals-Coll, 2012). Cognitive decline typically involves memory functions, as well as attention and executive functions (Peña-Casanova et al. 2012; Weintraub, Wicklund & Salmon, 2012). Difficulties in finding words and in communication, and problems in focusing, reasoning, planning and handling complex tasks arise (Peña-Casanova et al., 2012; Weintraub et al., 2012). Deficits in visual perception, coordination and motor functions may also be indications of neurodegeneration (Weintraub et al., 2012). Gradually, a person loses competence in skilled daily activities, such as driving, using a computer or a cell phone, cooking, and taking medication accurately. While progressing, disorientation and confusion may arise, and finally basic activities of performing self-care tasks are lost.

Neuropsychiatric symptoms of dementia include personality changes, depression, anxiety, and inappropriate behavior (Cummings, 2005; Finkel, 2001). Neuropsychiatric symptoms refer to behavioral and psychological changes that typically emerge in later stages of disease progression, but in some types of dementia changes in behavior, personality, and social dysfunction emerge at the early stage of the disease (Rascovsky et al., 2011). Later on, problems of sleep disturbance, wandering and agitation may interfere with daily life, and as the disease progresses more severe psychiatric symptoms (e.g. physical or verbal aggression, disruptive vocalization, paranoia) may arise (Finkel, 2001). Neuropsychiatric symptoms are often difficult to manage, can be an excessive burden to caregivers, and are among the main reasons for institutionalization (Yaffe et al., 2002).

Declining physical functioning is an inherent part of dementia progression. Physical frailty, gait disturbances and weight loss are all associated with dementia (Buchman, Schneuder, Leurgans & Bennett, 2008; Gillette Guyonnet et al., 2007). In later stages of dementia basic motor skills such as walking, chewing and swallowing may be impaired, and incontinence is frequent (Skelly & Flint, 1995).

2.1.3 Cost and burden of dementia

In full-blown dementia, the significant decline from previous levels of functioning leads to constant need of assistance and care, which enormously adds to the socioeconomic burden

of dementia. The estimated worldwide costs of dementia in 2015 were $818 billion, which represents an increase of 35% since 2010 (Wimo et al., 2017). The direct costs of institutional and social care contribute to a major proportion of the total costs, whereas the costs in the medical sector remain much lower (Wimo et al., 2017). In Finland, the mean annual health-care costs per case of dementia have been €20,000–25,000 (Eloniemi-Sulkava et al., 2009; Pitkälä et al., 2013). Costs increase with disease progression: a strong association has been found in AD between dependence on caregivers and total care costs (Lacey, Niecko, Leibman, Liu & Grundman, 2013).

While dementia shortens the lives of those affected, it also has a great impact on quality of life, both for individuals living with dementia, and for their families. It is estimated that family members care for up to 70% of patients with dementia at home (Lacey et al., 2013). In 2014, there were almost 24,000 caregivers over the age of 65 in Finland who had made an official agreement with the welfare state regarding compensation for taking care of their family member in need (Tikkanen, 2016). Caregivers help patients with activities of daily life, provide them with memory aids, and assist with exercise and other types of behavioral intervention. Dependency on a caregiver, depressive symptoms, and problematic forms of behavior add a burden to family caregivers, who experience increased emotional stress, depression and health problems (Mahoney, Rega, Katona & Livingston, 2005; Tremont, 2011). Effective methods for supporting the independence of patients during disease progression would alleviate the burden on caregivers.

2.2 Subtypes of dementia

2.2.1 Diagnostic criteria of dementia

Dementia is a condition caused by a cerebral disease, characterized by subtle onset and progressive disturbance of cognitive functions (e.g. memory, learning and language). Impairment in cognitive functioning is often accompanied by disorders of emotional and social behavior. The diagnostic criteria for dementia and its etiological subtypes have changed over time. Table 1 shows the current definition and common diagnostic criteria for major neurocognitive disorder (previously dementia) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association, APA, 2013), and for dementia according to the International Classification of Diseases, tenth edition (ICD-10; World Health Organization, WHO, 2016).

In both classification systems the core features include significant cognitive decline from a previous performance level, and its interference with daily functioning. Subtypes of dementia have diverse etiologies, and typical clinical characteristics. Therefore, each etiological entity, such as AD, is determined by specific diagnostic criteria (McKhann et al., 2011; WHO, 2016).

In clinical practice, the level of a patient's cognitive impairment is assessed, and dementia diagnosed using a combination of history-taking from the patient and his/her family, or other reliable informant, and an objective assessment of the patient's cognitive and somatic

status, mood, behavioral symptoms and physical functioning. Neuroimaging, laboratory tests and other biomarkers are used in diagnostics. Staging dementia severity as mild, moderate or severe is based on a patient's symptoms and functional abilities, and confirmed by using appropriate clinical rating scales (Sheehan, 2012).

Table 1. Definition of dementia (major neurocognitive disorder) according to ICD-10 (WHO, 2016) and DSM-5 (APA, 2013) classification systems.

ICD-10	**DSM-5**
Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairments of cognitive function may be accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. The syndrome occurs in Alzheimer's disease, in cerebrovascular disease, or in another condition primarily or secondarily affecting the brain.	Diagnosis of major neurocognitive disorder requires: • Evidence of substantial cognitive decline from a previous level of performance in one or more cognitive domains: learning and memory, language, executive ability, complex attention, perceptual-motor abilities, or social cognition. • Evidence of decline is based on concern of the individual, an informant, or the clinician, and impairment in cognitive performance is documented by clinical assessment. • The cognitive deficits interfere with independence in everyday activities. Assistance should be required at a minimum with complex activities of daily living, such as paying bills or managing medications. The cognitive deficits do not occur in the context of delirium, or another mental disorder (e.g. major depressive disorder, schizophrenia). Disorders are attributable to changes in brain structure, function, or chemistry. The etiology of the syndrome, when known, is to be coded as a subtype (e.g. Alzheimer's disease).

APA, American Psychiatric Association; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; ICD-10, International Classification of Diseases, Tenth edition; WHO, World Health Organization.

The clinical features and problems in various cognitive domains depend on the dementia subtypes, which are described in more detail in the following sections.

2.2.2 Alzheimer's disease

Alzheimer's disease accounts for an estimated 60–80% of dementia cases (Alzheimer's Association, 2018). It is characterized by progressive loss of synapses and neurons, with the accumulation of amyloid plaques, and neurofibrillary tangles in the brain (Braak & Braak, 1991; Serrano-Pozo, Frosch, Masliah & Hyman, 2011). The neuropathological changes begin

to emerge years or even decades prior to onset of the first clinical symptoms (Caselli, Beach, Knopman & Graff-Radford, 2017). The disease usually begins in medial temporal lobe structures, i.e. the hippocampus and entorhinal cortex, interfering with the neural network critical for episodic memory (Braak & Braak, 1991). Deficits in episodic memory are typically the earliest symptoms, and impaired ability to learn and retain new information begins to disrupt daily life (Albert, 2011). As the disease progresses, the pathology expands to other limbic and neocortical areas, causing deficits in other cognitive domains, and later on, emotional and behavioral problems (Braak & Braak, 1991; Förstl & Kurz, 1999).

The National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria to diagnose AD are used in clinical practice and research. These criteria were first set down in 1984 and revised in 2011 (McKhann et al., 1984, 2011). Despite memory problems, there should be evidence of cognitive dysfunction in one or more other cognitive domains in order to meet diagnostic criteria for probable AD dementia (McKhann et al., 2011).

2.2.3 Vascular dementia

Vascular dementia is the second most common type of major neurodegenerative disease in older adults, accounting for 15% of dementia cases (O'Brian et al., 2003; O'Brian & Thomas, 2015). The term 'vascular dementia' refers to a severe form of vascular cognitive impairment (VCI), i.e. cognitive impairment caused by a cerebrovascular disease. The main subtypes of VCI include cortical large-vessel disease, subcortical small-vessel disease, and conditions due to an infarct in a critical area for information processing (Rockwood, 2002).

Diagnosis of vascular dementia requires cognitive decline verified by way of a standardized cognitive test or scale, evidence of an associated vascular brain lesion, and exclusion of reversible causes of cognitive decline (Román et al., 1993). The Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke, and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria emphasize the heterogeneity of vascular dementia syndromes and pathologic subtypes; variability in the clinical course of vascular dementia; specific clinical findings early in the course (e.g. gait disorder, incontinence, mood and personality changes); the need to establish a temporal relationship between stroke and dementia onset; the importance of brain imaging to support clinical findings; and the value of neuropsychological testing to show impairments in multiple cognitive domains (Román et al., 1993).

2.2.4 Dementia with Lewy bodies and Parkinson's disease dementia

Dementia with Lewy bodies and Parkinson's disease dementia, called Lewy body dementias, share the same pathophysiology, and are the second most common type of degenerative dementia in patients older than 65 years (Walker, Possin, Boeve & Aarsland, 2015). In one study, in a population aged 75 years and older, Lewy body dementias accounted for 22% of all demented subjects (Rahkonen et al., 2003). The hallmarks of Lewy body dementias are α-

synuclein neuronal inclusions (Lewy bodies and Lewy neurites), accompanied by neuronal loss (Walker et al., 2015). The main characteristics of Lewy body dementia are the presence of visual hallucinations, fluctuations of symptoms and parkinsonian features (McKeith et al., 2005). Deficits in attention, executive function, and visuospatial ability may be especially prominent (McKeith et al., 2005).

Parkinson's disease dementia is a dementia syndrome where cognitive decline emerges within the context of established Parkinson's disease (Emre et al., 2007). A community-based study revealed an estimated point-prevalence of dementia in Parkinson's disease to be around 25% (Aarsland, Tandberg, Larsen & Cummings, 1996). Increasing age is a risk factor of the development of dementia in patients with Parkinson's disease (Walker et al., 2015). Clinical features include impairment in attention, executive functions, mental speed, visuospatial functions, and/or memory, where recognition is usually better than free recall and performance usually improves with cueing (Emre et al., 2007). Dementia with Lewy bodies and Parkinson's disease dementia are syndromes that share many clinical features, genetics, and neuropathology, and may be viewed as extremes on a continuum (Jellinger & Korczyn, 2018; Walker et al., 2015).

2.2.5 Mixed and other types of dementia

The most common etiologies, AD, vascular dementia, and dementia with Lewy bodies, account for up to 90% of all dementia cases (O'Brian et al., 2003; Ott et al., 1995; Sheehan, 2012). The boundaries between different forms of dementia are imprecise, and mixed types often exist (Schneider, Arvanitakis, Bang & Bennet, 2007). The likelihood of having mixed dementia increases with age, and mixed brain pathologies may account for more than 50% of dementia cases in community-dwelling older persons (Schneider et al., 2007). In the most common form of mixed dementia the abnormal protein deposits of AD coexist with blood-vessel problems linked to vascular dementia (Langa, Foster & Larson, 2004). Alzheimer's brain changes also often coexist with Lewy body neuropathology (Schneider et al., 2007).

Frontotemporal lobar degeneration is a clinically, genetically, and pathologically heterogeneous group of progressive diseases (Bang, Spina & Miller, 2015). Degeneration typically emerges in patients less than 65 years of age (Pasquier, Richard & Lebert, 2004). The disease is associated with prominent atrophy of the frontal and temporal lobes of the brain, and the clinical phenotype depends on the primary site of brain dysfunction (Mackenzie et al., 2010; Rascovsky et al., 2011). Frontotemporal lobar degeneration is characterized by progressive deficits in behavior (e.g. personality changes, disinhibition, and apathy), executive function, and language (Bang et al., 2015). It accounts for approximately 5-10% of all dementia cases (Barker et al., 2002).

Other rare disorders that can lead to progressive dementia are, for example, normal-pressure hydrocephalus, Huntington's disease and Creutzfeld-Jacob disease.

2.3 Cognition in dementia

The neuropsychological profile of dementia comprises both cognitive and behavioral symptoms, the most common ones being memory loss, problems with attention, executive function, language, and changes in mood and personality. The prominence of symptoms varies from person to person, and also depends on the course and stage of the dementia subtype. In clinical practice, as well as in research, cognition is considered to be the key factor to observe in individuals with dementia (Sheehan, 2012).

2.3.1 Evaluation of cognition

Subjective concern is an important but insufficient source of information when diagnosing cognitive decline in a person. Global cognitive scales (e.g. the Mini-Mental State Examination, MMSE; Folstein, Folstein & McHugh, 1975), and test batteries, such as the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Sotaniemi et al., 2012) are widely used tools for screening cognitive status of a patient both in clinical and research settings. The Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog; Rosen, Mohs & Davis, 1984) is a similarly common scale in clinical trials to determine the rate of cognitive decline. The purpose of any assessment scale is to increase the precision of evaluation by reducing subjectivity and increasing objectivity of the observations and conclusions (Sheehan, 2012).

Global cognitive scales and short test batteries are usually sensitive enough to diagnose dementia when combined with clinical interview, a carefully examined medical history, physical and neurological examination, appropriate laboratory investigations, and brain imaging (Hugo & Ganguli, 2014). Neuropsychological assessment is recommended when routine history and global measures of cognitive status cannot provide reliable evidence of cognitive decline.

2.3.2 Cognitive deterioration in dementia

Subtle cognitive deficits are often the first signs of underlying neuropathology, especially in AD, where the disease typically begins with mild but detectable deficits (Albert, 2011; Bäckman, Small & Fratiglioni, 2001). In the mild stage of dementia cognitive symptoms typically prevail in the clinical picture. As the disease progresses, early cognitive symptoms intensify and eventually broadly affect the person's ability to remember, communicate and function independently. At the late stages of dementia, specific cognitive deficits can no longer be disentangled, while almost all cognitive functions have been severely impaired (Förstl & Kurz, 1999).

Cognitive decline may begin many years before diagnosis of the disease (Wilson et al., 2012). In AD, for example, the first signs in episodic memory may remain stable for years (Bäckman et al., 2001). Likewise, a decline in measures of semantic memory and conceptual formation may be detected as early as 12 years before AD diagnosis (Amieva et al., 2008). In

early stages of AD, memory loss in new learning and delayed recall of visual and/or verbal material predominates, while short-term memory, declarative memory from the patient's earlier years, and implicit memory are affected to a much lesser degree (Förstl & Kurz, 1999). Attention and executive difficulties have been suggested to be the first non-memory cognitive domains to be affected, before deficits in language and visuospatial functions emerge (Perry & Hodges, 1999). In atypical variants of AD, however, problems of word-finding, visuospatial cognition, object agnosia, and executive functioning already predominate in the clinical picture in the early stages of the disease (McKhann et al., 2011; Peña-Casanova et al., 2012).

Vascular cognitive impairment may involve mild symptoms restricted to one or more areas of information processing, or progressive states where extensive symptoms lead to severe memory disorder and vascular dementia (O'Brian et al., 2003; O'Brian & Thomas, 2015). Given the variability of vascular lesions and locations, the symptoms and their time courses are often variable; the progression of cognitive decline can be in a stepwise pattern, show a more gradual pattern, or can be fluctuating or rapid in its course (Hugo & Ganguli, 2014). Vascular dementia has been proposed to include early impairment of attention and executive function, slowing of motor performance and information processing, and relatively spared episodic memory compared with that in AD (O'Brian et al., 2003). Similarly, in Lewy body dementias, deficits in tests of attention, executive function and visuospatial ability are especially prominent, and memory deficit is particularly notable in free recall of information (Emre et al., 2007; McKeith et al., 2005).

While many neurodegenerative diseases affect memory, some forms of dementia do not initially involve memory loss. Frontotemporal lobar degeneration typically interferes with executive functioning and ability to use language (Bang et al., 2015). Progressive deficits in speech, grammar, and word output may predominate, as well as disorders of semantic knowledge and naming (Bang et al., 2015). At the early stage of behavioral-variant frontotemporal dementia, profound neuropsychiatric symptoms predominate over cognitive deficits (Ranasinghe et al., 2016). Figure 1 summarizes the predominant neuropsychological findings in the most common types of dementia.

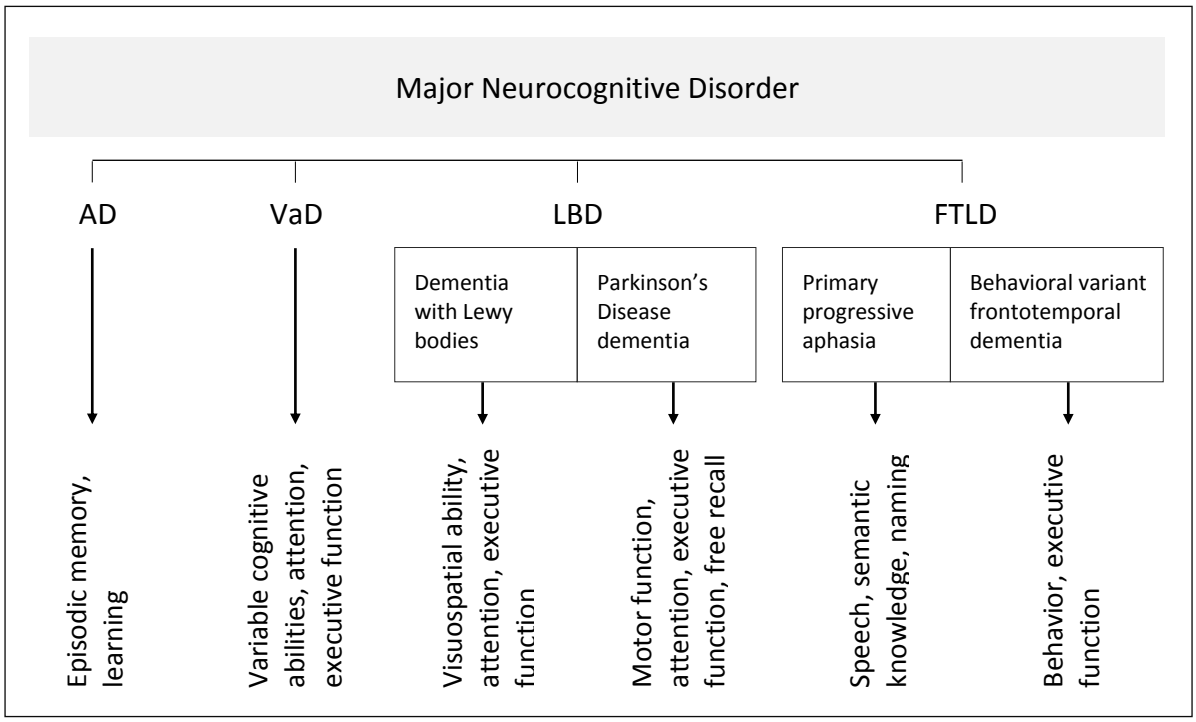

Figure 1. The main neuropsychological functions affected in major neurocognitive disorders, i.e. Alzheimer's disease (AD), vascular dementia (VaD), Lewy body dementias (LBD) and frontotemporal lobar degeneration (FTLD).

2.4 Treatment of dementia

Currently available therapies cannot reverse the pathologic processes of major neurocognitive disorders. Management of dementia is focused on the symptoms of a patient, and guided by the stage of the illness. At present, the main treatment objectives are to maintain prevailing cognitive and functional ability, minimize behavioral disturbances, and slow disease progression (Sadowsky & Galvin, 2012). While the number of patients with dementia is growing, novel and cost-effective treatment methods are necessitated.

2.4.1 Medication

Clinical trials in AD have been focused on drugs that increase the levels of acetylcholine in the brain to compensate for losses of cholinergic function. Acetylcholine esterase inhibitors (AChEIs) represent first-line therapy for patients with AD, whereas a glutamate N-methyl D-aspartate (NMDA) receptor antagonist is used in the treatment of more advanced stages of AD (Sadowsky & Galvin, 2012). AChEI treatment with donepezil, rivastigmine and galantamine has been found to be clinically effective in mild to moderate cases of AD (Birks, Grimley Evans, Iakovidou, Tsolaki & Holt, 2009; Birks & Harvey, 2018; Tan et al., 2014). When the disease progresses beyond the moderate stages, these drugs tend to lose their effects (Nelson & Tabet, 2015). Memantine is used for the treatment of moderate to severe AD, either alone or in combination with with AChEI treatment (Sadowsky & Galvin, 2012).

At best, current forms of medication can slow the progression of the disease (Gillette-Guyonnet et al., 2011). Findings on amyloid-lowering drugs, T-cell-based and neuroprotective approaches so far are preliminary (Nelson & Tabet, 2015).

Although primarily used to treat AD, cholinesterase inhibitors may also be prescribed for other dementias, including vascular dementia, Parkinson's disease dementia and Lewy body dementia, but to date with few benefits (O'Brien & Thomas, 2015; Stinton et al., 2015). Moreover, rivastigmine has been suggested to be beneficial in Parkinson's disease dementia and subcortical vascular dementia (Kandiah et al., 2017).

Pharmacological treatment of neuropsychiatric symptoms is necessary when non-pharmacological therapies fail to reduce behavioral and psychological symptoms (Sadowsky & Galvin, 2012; Schneider et al., 2005). Antipsychotic drugs, and treatment of depression and sleep disturbances may have a positive impact on dementia symptoms, although the effects appear to be limited, and risks of adverse effects, even stroke and increased mortality, are high in frail older persons (Schneider et al., 2005; Wang et al., 2015). Furthermore, patients with Lewy body dementia can develop severe sensitivity to conventional neuroleptics, and care should be taken to identify the type of dementia when using antipsychotics (Walker et al., 2015).

2.4.2 Diversity of non-pharmacological treatments

A number of non-pharmacological therapies are currently suggested for people with dementia, including proper diet, nutritional supplements, physical exercise, psychosocial interventions, reminiscence, music therapy, training in activities of daily living (ADL), and cognition-focused approaches. Each therapy is rarely offered in isolation, and treatment of dementia is leaning towards a multidimensional approach. The aim of an offered treatment may be delay of institutionalization, improvement in or preservation of patients' cognition, functional abilities, psychological well-being, mood, and/or quality of life, plus prevention or alleviation of behavioral symptoms, as well as improvement in well-being, mood and quality of life among caregivers (Olazarán et al. 2010).

Clinical trials have mainly been focused on AD, where beneficial effects have been associated with dietary interventions, physical exercise, and cognitive stimulation offered in groups (Nelson & Tabet, 2015). Adherence to a Mediterranean-style diet has been associated with slower rates of cognitive decline and reduced conversion to AD in patients with mild cognitive impairment (Hardman, Kennedy, Macpherson, Scholey & Pipingas, 2016). Nutritional guidance is reported to enhance nutrition and quality of life, and to prevent falls among community-dwelling people with AD (Suominen et al., 2015). A study on multinutrient medical food revealed a positive effect on cognition in cases of mild AD (Scheltens et al., 2012), whereas in another study the same product did not slow cognitive decline in persons at a mild or moderate stage of AD (Shah et al., 2013). Antioxidants and fatty fish intake have been suggested to be protective against vascular dementia risk (Perez, Helm, Sherzai, Jaceldo-Siegl & Sherzai, 2012).

Physical exercise represents a potential non-pharmacological treatment to alleviate symptoms of dementia or delay its progression (Groot et al., 2016). Exercise has direct positive effects on the brain, probably through improving vascular health (Haskell et al., 2007). Exercise may also be influential in preserving neuronal structures, and promoting neurogenesis (Colcombe & Kramer, 2003). In a recent Finnish Alzheimer Disease Exercise Trial (FINALEX) regular and long-term home-based exercise improved cognition among community-dwelling older people with AD (Öhman et al., 2016). Home-based exercise took place twice a week for one hour over 12 months under the supervision of a physiotherapist, and a positive effect was found on executive function when compared with a control group under usual care (Öhman et al., 2016).

Social stimulation is associated with positive cognitive and emotional responses in older people (Kelly et al., 2017), as well as reduced use of health services (Pitkälä, Routasalo, Kautiainen & Tilvis, 2009). Lack of social networks, and living alone has been shown to increase the risk of dementia (Fratiglioni, Wang, Ericsson, Maytan & Winblad, 2000). A recent synthesis of systematic reviews on psychosocial treatment in dementia suggests that interventions with strong social elements might be beneficial for mood, social interaction and quality of life (QoL) (McDermott et al., 2018). Moreover, in another study, group rehabilitation to enhance self-efficacy and problem-solving skills of the participants had beneficial effects on cognition of persons with dementia (Laakkonen et al., 2016). To date, the most consistent evidence for an association between social engagement and improvement in cognitive functioning comes from RCTs concerning group-based cognitive stimulation (Huntley et al., 2015; Woods, Aguirre, Spector & Orrell, 2012). In addition, regular musical activities (singing and listening to music) have been suggested to maintain or enhance general cognition, orientation, attention and executive function, and remote personal episodic memory of persons with dementia, as well as to improve their mood (Särkämö et al., 2014).

2.4.3 Cognition-focused approaches

Cognitive enhancement, in general, refers to behavioral treatment of cognitive deficits through the practice of compensatory or restorative strategies, or both (Choi & Twamley et al., 2013). Cognition-focused interventions for patients with dementia have diversified during the evolution of non-pharmacological treatments. Different intervention strategies and concepts have been used almost interchangeably in the past, and the same lack of precision in categorizing cognitive interventions is still present in many clinical trials. Furthermore, many cognition-focused intervention programs combine CT techniques with other methods of rehabilitation, adding to ambiguity when drawing conclusions on the efficacy and effectiveness of specific approaches.

In this study a widely accepted classification by Clare and Woods (2004) is adopted, where cognition-focused approaches are grouped into three types of intervention: cognitive stimulation, CT and cognitive rehabilitation. The three approaches are each based on different theoretical constructs of restoration and compensation (Choi & Twamley, 2013;

Clare & Woods, 2004). The aim of *cognitive stimulation* is general enhancement of cognitive and social functioning (Clare & Woods, 2004). It is usually administered in a group setting, is often recreational in nature, and involves non-specific cognitive activities and discussions. Reality orientation and reminiscence are examples of specific cognitive-stimulation techniques (Spector et al., 2003; Woods, Spector, Jones, Orrell & Davies, 2005). Several RCTs have been carried out to evaluate the effects of cognitive stimulation in AD and other types of dementia, and the results suggest a positive effect on general cognitive functioning, and QoL of patients (Huntley et al., 2015; Woods et al., 2012; Piras et al., 2017).

Cognitive training is defined as guided practice in a set of standard tasks designed to reflect particular cognitive functions such as memory, attention or executive functions (Clare & Woods, 2004). CT is assumed to improve, or at least stabilize performance in a given cognitive domain (i.e. a near-transfer effect). In addition, generalized effects (i.e. far-transfer effects) beyond the immediate training context are expected (Clare & Woods, 2004; Zelinski 2009). Targeted CT is based on the principles of restoration of impaired cognitive function, whereas compensatory CT utilizes behavioral strategies to overcome cognitive deficits and associated functional disabilities. Training is typically offered either in an individual or a group format using pre-designed paper-and-pencil exercises or computerized programs with various levels of difficulty.

Since the earliest clinical trials in the 1980s, an increasing number of studies have been conducted on the efficacy of CT in dementia. The effects have been summarized in systematic reviews encompassing patients with dementia (Kurz et al., 2011; Spector, Orrell & Hall, 2012), patients with AD (Huntley et al. 2015; Oltra-Cucarella, Perez-Elvira, Espert & Sohn McCormick, 2016), and patients with AD or vascular dementia (Bahar-Fuchs et al., 2013), and are further discussed in Section 2.6 of this report. Briefly, the findings to date have been promising in some trials, but often mixed and inconsistent.

Cognitive rehabilitation refers to a more individualized approach where personally relevant goals are identified, and the therapist works with a person and his or her family to discover strategies to address the selected goals (Clare & Woods, 2004). The focus is more on compensation and far-transfer effects of rehabilitation, than on specific cognitive abilities. Multiple training methods and compensatory strategies are used for managing dementia symptoms and increasing the capacity to perform daily activities. Only a few trials have concerned the effects of cognitive rehabilitation among patients with dementia. However, Clare et al. (2010) suggested clinical efficacy in helping patients with their goal achievement after eight weekly sessions of individualized rehabilitation, which Kim (2015) replicated a few years later. A large-scale RCT revealed lower functional disability and a six-month delay in institutionalization at two years among a group of persons with mild to moderate AD who attended individualized cognitive rehabilitation for 24 months (Amieva et al., 2016).

2.4.4 Multicomponent interventions

While pharmacotherapies are a routine treatment choice in several types of dementia, up-to-date dementia care utilizes supplementary non-pharmacological approaches (Memory

Disorders: Current Care Guidelines, 2017). The effects of multicomponent interventions have been examined in several RCTs, where CT has been combined with psychomotor activities (Olazarán et al., 2004), ADL training (Bottino et al., 2005; Fernández-Calvo et al., 2015; Olazarán et al., 2004), physical activity (Maci et al., 2012), reminiscence therapy (Barban et al., 2016) and other non-specific cognitive-stimulation methods (Barban et al., 2016; Bottino et al., 2005; Fernández-Calvo et al., 2015; Maci et al., 2012; Olazarán et al., 2004). A beneficial effect after multicomponent intervention has most often been shown on global cognition of patients with dementia (Barban et al., 2016; Bottino et al., 2005; Fernández-Calvo et al., 2015; Olazarán et al., 2004).

In addition to dementia care, multicomponent interventions have been examined in the prevention of dementia. For example, a large-scale Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) concerned the effects of multidomain intervention (diet, exercise, vascular-risk monitoring and CT) among 1260 older adults at risk of cognitive decline (Ngandu et al., 2015). The participants in the intervention group were able to improve or at least maintain their cognitive functioning during the 2-year intervention (Ngandu et al., 2015).

2.5 Cognitive training and the brain

Cognitive training, or *brain training*, has become a 'hot' topic in aging populations. The possibility of cognitive enhancement by training the adult brain has substantially raised public interest in targeted cognitive interventions. At the same time modern technologies and web-based applications increase the accessibility of these tasks.

A possible brain mechanism to mediate a positive training effect is neuroplasticity. Plasticity refers to the ability of the brain to form and reorganize neural connections, especially in response to learning, or following a brain injury. Neural plasticity is present not only in the developing brain, but also in the adult brain, as reviewed by Rabipour and Raz (2012). A well-known study on London taxi drivers showed that repeated practice of skills required for navigating in London induces lasting changes within the hippocampal gray matter volume (Maguire, Woollet & Spiers, 2006). Similarly, there is large amount of evidence of structural and functional plasticity induced by musical training in the human brain (Herholz & Zatorre, 2012). Furthermore, structural plasticity has been found in the aging brain. In a juggling-training study, motor-skill acquisition was related to gray-matter changes in participants around 60 years of age, although the effect was slightly smaller than in a group of 20-year-old subjects (Boyke, Driemeyer, Gaser, Buchel & May, 2008).

The effects of CT among healthy older adults have been widely studied and reviewed, with some positive findings (e.g. Butler et al., 2018; Lampit, Hallock & Valenzuela, 2014; Rejnders, van Heugten & van Boxtel, 2013). Training seems to improve cognitive performance in the domain-trained, but otherwise there have been few benefits to report. Generalization in terms of far-transfer effects has often been limited (Rabipour & Raz, 2012; van Heugten, Ponds & Kessels, 2016). However, a large RCT on 487 community-dwelling older adults (65 and older) did show that a training program designed to improve the speed

and accuracy of auditory information processing has benefits that generalize to untrained measures of memory and attention (Smith et al., 2009).

In another large-scale and long-term RCT, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE), 2832 healthy older adults were allocated randomly to one of three training groups, or to a control group (Ball et al., 2002). Ten CT sessions were provided for verbal episodic memory, inductive reasoning, or processing speed, and post-training improvements were seen in specific targeted skills that lasted for two years. The 5-year follow-up showed that two 4-session booster treatments resulted in maintenance of treatment gains on the trained cognitive domains. However, less functional decline in self-reported instrumental activities of daily living (IADL) was found only in the reasoning training group (Willis et al., 2006). CT did not affect rates of incident dementia after five years of follow-up (Unverzagt et al., 2012), but both processing speed and reasoning training reduced motor vehicle collision risk over the subsequent period of six years (Ball, Edwards, Ross & McGwin, 2010). Some beneficial effects were maintained ten years after the initial training (Rebok et al., 2014).

Treatment of injured brain function relies in general on principles of targeted training and compensatory approaches (Cicerone et al., 2011; Rabipour & Raz 2012; Robertson & Murre, 1999). In patients with dementia, significantly impaired episodic memory limits overt teaching of compensatory strategies at a behavioral level, and therefore CT gains should rely more on implicit learning and memory through repetitive practice. Possible treatment gains might be related to functional plasticity, in other words to a training-related increase (or decrease) in the activity of the brain (Belleville et al., 2011; Grady et al., 2003; Spironelli, Bergamaschi, Mondini, Villani & Angrilli, 2013; van Paasschen et al., 2013). In a recent study, Barban et al. (2017) showed specific attentional improvements and associated functional changes in the brain after a 3-month period of computerized CT among a small group of patients with mild AD (Barban et al., 2017). However, due to the lack of significant correlations between neuroimaging and cognitive data, the findings remain speculative (Barban et al., 2017).

Another possible mechanism for training gains in dementia might be increased cognitive reserve (Stern, 2012). It has been suggested that cognitive reserve is not a fixed factor at older age, but that it can be modified by environment and life experience throughout the course of life, and possibly offer resilience to neuropathology even when the brain is already affected by a disease (Liberati, Raffone & Belardinelli, 2012).

2.6 Effects of cognitive training in older adults with dementia

The numerous clinical trials on CT in dementia have evolved from the first '*in vivo*' studies conducted at treatment facilities to a few large-scale and well-controlled trials conducted at more than one medical center or clinic. In an early review CT was suggested to be promising in the treatment of AD (Sitzer, Twamley & Jeste, 2006), but later reviews and meta-analyses have indicated that the current evidence is miscellaneous and insufficient (Bahar-Fuchs et al., 2013; Huntley et al., 2015; Kurz et al., 2011; Oltra-Cucarell et al., 2016; Spector et al., 2012).

A Cochrane review published in 2013 concerned 11 RCTs (n = 486) on the effects of CT in dementia due to Alzheimer's and vascular disease, and one RCT (n = 69) on cognitive rehabilitation (Bahar-Fuchs et al., 2013). The studies were relatively small; from 11 to 103 participants. Program length varied from five to 24 weeks, and training was most often conducted on an individual basis. The review revealed no clear evidence of benefits of CT in dementia. However, the authors stated that the quality of the studies was generally not high, and well-designed studies of CT are needed to obtain more definitive evidence (Bahar-Fuchs et al., 2013). Since the Cochrane review and subsequent meta-analyses a substantial amount of new studies have been published on the effects of restorative and/or compensatory CT in dementia.

2.6.1 Effects on cognition

The most common finding in RCTs on CT in dementia is a slight improvement in cognitive status among persons with dementia (usually AD) as measured by using the MMSE immediately after a period of training (Bergamaschi et al., 2013; Breuil et al., 1994; De Luca et al., 2016; Gaitán et al., 2013; Galante, Venturini & Fiaccadori, 2007; Huntley, Hampshire, Bor, Owen & Howard, 2017; Jelcic et al., 2012; Jelcic et al., 2014; Kawashima et al., 2005; Loewenstein, Acevedo, Czaja & Duara, 2004; Niu, Tan, Guan, Zhang & Wang, 2010; Tárraga et al., 2006; Trebbastoni et al., 2018). Table 2 shows the details of these trials, as well as the eight additional RCTs that failed to show a benefit as regards global cognitive status (Bourgeois et al., 2016; Davis, Massman & Doody, 2001; Giuli, Papa, Lattanzio & Postacchini, 2016; Heiss, Kessler, Mielke, Szelies & Herholz, 1994; Koltai, Welsh-Bohmer & Schmechel, 2001; Kurz et al., 2012; Lee, Yip, Yu & Man, 2013; Voigt-Radloff et al., 2017).

Another common tool in clinical trials is ADAS-Cog, which was developed primarily as an index of global cognitive functioning (Rosen et al., 1984). A beneficial effect among patients with dementia on global cognition measured by way of ADAS-Cog has been reported after interactive multimedia intervention for 24 weeks (Tárraga et al., 2006), adaptive working memory training for eight weeks (Huntley et al., 2017), and a 10-week intervention combining restorative and comprehensive approaches (Giuli et al., 2016). However, none of the three studies covered maintenance of the training effect. Furthermore, a large-scale multicenter trial failed to show an effect of CT on global cognition after three months of weekly training, and 21 months of booster training, meaning a session once every six weeks (Amieva et al., 2016) (Table 2).

Tests measuring participants' cognitive status or global cognition have been more frequently used in CT trials than tests covering specific cognitive domains. Positive findings concerning *episodic memory* (Cavallo, Hunter, van der Hiele & Angilletta, 2016; Giovagnoli et al., 2017; Huntley et al., 2017; Jelcic et al., 2012, 2014; Lalanne, Gallarda & Piolino, 2013; Loewenstein et al., 2004; Neely, Vikström & Josephsson, 2009; Quayhagen, Quayhagen, Corbeil, Roth & Rodgers, 1995; Quayhagen et al., 2000; Tappen & Hain, 2014; Trebbastoni et al., 2018), *language abilities* (Bergamaschi et al., 2013; Cavallo et al., 2016; Giovagnoli et al., 2017; Giuli et al., 2016; Jelcic et al., 2012, 2014; Quayhagen et al., 1995, 2000; Trebbastoni et

al., 2018), *working memory* (Bergamaschi et al., 2013; Cavallo et al., 2016; Giuli et al., 2016; Huntley et al., 2017; Trebbastoni et al., 2018), and a few times also concerning *executive function* (Bergamaschi et al., 2013; Cavallo et al., 2016; Gaitán et al., 2013; Kawashima et al., 2005), *attention* (De Luca et al., 2016; Giuli et al., 2016; Loewenstein et al., 2004), *visual peception* (Bergamaschi et al., 2013) and *constructional apraxia* (De Luca et al., 2016) have been reported. However, several studies have been significantly limited by small sample sizes, reduced statistical power, and non-robust statistical analyses. In addition, the use of multiple outcome measures has increased the risk of false-positive findings in many trials.

An improvement in a training-specific outcome is a typical finding in RCTs on CT in dementia. For example, benefits have been reported in connection with home-based daily training of caregiver-patient dyads, focusing on memory, problem solving and conversational fluency, and there was increased performance in delayed memory, problem solving and verbal fluency in stimulated patients with dementia, whereas less change was observed in other study groups (Quayhagen et al., 2000). Improvement in language abilities, verbal memory and global cognition was indicated after 3-month lexical-semantic stimulation in a group of patients with mild AD (Jelcic et al., 2012). Face-name associations and working out change for a purchase improved compared with active controls after training such abilities (Loewenstein et al., 2004; Tappen and Hain 2014). Lalanne et al. (2015) observed a positive impact on both semantic and episodic autobiographical memory after an individualized memory program, where training in these aspects of memory was carried out for six weeks. Likewise, Neely et al. (2009) arranged 8-week practice of memory strategies for dementia patients and their spousal caregivers, and reported improvement in the recall of categorizable words. Despite these cautiously promising findings, generalization of the training effects to other cognitive abilities, or daily activities, has been rarely reported.

Technological advances have increased the popularity of computerized interventions, and evidence of the effects of computerized cognitive training (CCT) among patients with dementia is growing (Cavallo et al., 2016; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Heiss et al., 1994; Lee et al., 2013; Pietilä et al., 2017; Tárraga et al., 2006; Zhuang et al., 2013). Table 2 shows details of RCTs involving CCT, including five reports of a positive training effect in cognition (Cavallo et al., 2016; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Tárraga et al., 2006). Older adults might be more familiar with traditional pen-and-paper exercises, however, and trials with CCT have typically involved populations younger than 80 years of age.

The effects of intervention are commonly measured post-intervention, and occasionally followed up after later. In previous trials concerning CT in dementia, the post-intervention follow-up period has varied from only a few weeks to a maximum of nine months (Gaitán et al., 2013). In cases of major neurodegenerative disorders, maintenance of a cognitive benefit should be an important goal when trying to affect disease progression.

Table 2. Effects of cognitive training on cognition in patients with dementia.

Trial **Sample size**	**Participants**[1]	**Interventions**	**Assessment time** **Effect on cognition**	**Efficacy**[2]	**Quality rating**[3] **Comments**
Studies on restorative cognitive training					
Amieva et al. 2016 France *n* = 653	AD F 60% 79 years MMSE 22	IG, *n* =170; Cognitive training therapy designed to involve various cognitive functions (memory, attention, language, and executive function); 90 min, 1/week, 3 months, then 90 min, 1/6 weeks, 21 months; In groups CG, *n* = 154; TAU	3 months (PI), 24 months (PI) ADAS-Cog: No differences between groups	-	High (9/10) Multicenter RCT Lost to F/U 28%
Beck et al. 1988 USA *n* = 20	AD or mixed dementia F 60% 75 years MMSE 15-20	IG, *n* = 10; Cognitive skills remediation training in attention, reading, concentrating on detail and remembering; 30-40 min, 3/week, 6 weeks; Individual CG, *n* = 10; TAU	6 weeks (PI) Attention and reading, Remembering digits, Story recall, Concentrating on detail: No significant differences between groups (reports improvement in IG on Remembering digits at $p = 0.10$)	-	Low (2/10) Pilot study
Bergamaschi et al. 2013 Italy *n* = 32	AD F not reported 78 years MMSE 21	IG, *n* = 16; Cognitive training in spatial orientation, memory, attention, perception, visual analysis, and recognition of emotional expressions; Five cycles of 120 min, 5/week, 4 weeks; In groups CG, *n* = 16; Daily non-specific cognitive activity at a day centre; In groups	1 year (PI) MMSE, MODA, Memory test with interference, Verbal fluency, Overlapping figure test, Clock drawing test: Improvement in IG compared to a decline in CG Story recall: No differences between groups	++	Moderate (7/10)
Breuil et al. 1994 France *n* = 61	AD (92%) or other dementia F 61 % 77 years MMSE > 9	IG, *n* = 32; Global cerebral stimulation using mental imagery in its visual and semantic modes to stimulate encoding, consolidation and retrieval of information; 60 min, 2/week, 5 weeks; In groups CG, *n* = 29; TAU	6 weeks (PI) MMSE: Improvement in IG compared to CG CERAD Word list memory, Verbal fluency: No differences between the groups	+	Low (4/10) Five cognitive outcomes discarded due to a ceiling/floor effect
Cavallo et al. 2016 Italy *n* = 80	AD F 64% 76 years MMSE 23	IG, *n* = 40; Computerized cognitive training (the software Brainer1) in memory, attention, executive function, and language CG, *n* = 40; Non-specific use of a computer with an interventionist Both groups 30 min, 3/week, 12 weeks; Individual	3 months (PI), 9 months Digit span, Two-syllable words test, RBMT story test, Token, Brixton: Improvement in IG compared to CG at PI; Stability in IG at 9 months MMSE, RBMT profile score, Naming test, Verbal fluency, VOSP, Hayling test: No differences between groups	++	High (8/10)

Davis et al. 2001 USA *n* = 37	AD F 57% 71 years MMSE 22	IG, *n* = 19; Cognitive training in spaced retrieval of personal information, face-name associations and mnemonic strategy; 60 min, 1/week, 5 weeks; Individual + In-home attention process training directed by a caregiver; 30 min, 6/week, 5 weeks CG, *n* = 18; Unstructured conversation and psychoeducation; 60 min, 1/week, 5 weeks	5 weeks (PI) MMSE, WMS-R Logical memory and Visual Reproduction, Digit Span, Verbal Series Attention test, COWA, Category fluency: No differences between groups Within IG an enhanced recall of personal information and face-name associations during the 5-week intervention	-	Low (4/10)
De Luca et al. 2016 Italy *n* = 20	Vascular dementia F 5 % 78 years MMSE 25	IG, *n* = 10; Web-based rehabilitative program on praxis, attention, visual-spatial memory and verbal fluency; 45 min, 3/week, 8 weeks; Individual CG, *n* = 10; Standard neurorehabilitation	8 weeks (PI) MMSE, Attentive matrices, Constructional apraxia: Improvement in IG, no change in CG Category verbal fluency, Letter verbal fluency: No differences between groups	++	Low (3/10)
Gaitán et al. 2013 Spain *n* = 60	AD or MCI F 51% 76 years MMSE 25	IG, *n* = 23; Computer-based cognitive training in attention, memory and executive function; 60 min, 2-3/week, 12 weeks; Individual + Traditional pen-and-paper exercises for 12 months CG, *n* = 16; Traditional pen-and-paper exercises; 60 min, 2-3/week, 12 months; In groups	3 month (PI), 1 year MMSE: Slower deterioration in IG compared to CG over one year Iowa Gambling Task: Less disadvantageous choices in IG compared to CG at one year Composite scores of Attention and processing speed, Working memory, Memory, Executive function, Orientation, Praxias and gnosias, and Memory Failures in Everyday Memory: No differences between groups	++	Moderate (6/10) Lost to F/U 35%
Galante et al. 2007 Italy *n* = 11	AD F not reported 76 years MMSE 23	IG, *n* = 7; Computer-based cognitive intervention covering attention, perception, memory, language and spatial cognition CG, *n* = 4; Semi-structured interviews on current topics and life events Both groups 60 min, 3/week, 4 weeks; Individual	4 weeks (PI), 3 months, 9 months: MMSE only MMSE: Stability in IG compared to a decline in CG at 9 months MODA, Bisyllabic word repetition test, Prose memory, Corsi's block, Digit cancellation test, CPM, Verbal fluency, Denomination: No differences between groups at PI or 3 months	+	Low (4/10) Preliminary data on 11 participants

Giovagnoli et al. 2017 Italy *n* = 50	Probable AD F 61% 74 years MMSE 23	IG, *n* = 13; Cognitive training using verbal and visuospatial stimuli and answering questions CG1, *n* = 13; Active music therapy Both groups 45 min, 2/week, 12 weeks; In groups CG2, *n* = 13; Neuroeducation; 3 sessions, 3 months; In groups	12 weeks (PI), 24 weeks Word fluency (phonemic): Improvement in IG and stability in other groups at PI Short Story test: Stability in IG and CG1, decline in CG2 at PI Other 11 cognitive outcomes: No differences between IG and CGs	++	Moderate (6/10) Lost to F/U 22%
Giuli et al. 2016 Italy *n* = 101	AD F 66% 78 years MMSE 20	IG, *n* = 48; Cognitive training for attention, orientation, episodic and prospective memory and planning (restorative and compensatory approaches); 45 min, 1/week, 10 weeks; Individual + Daily homework with the help and support of a caregiver CG, *n* = 47; TAU including general psychoeducation	10 weeks (PI) ADAS, Verbal digit span, Semantic word fluency, Attentive matrices: Improvement in IG compared to CG MMSE, Prose memory test, Word pairing learning test, Supra-span of Corsi: No differences between groups	++	Moderate (5/10)
Heiss et al. 1994 Germany *n* = 70	AD F 47% 67 years MMSE 21	IG, *n* = 18; CCT using memory, perceptual and motor tasks; IG2, *n* = 17; CCT + pharmacological treatment of pyritinol; IG3, *n* = 18; CCT + pharmacological treatment of phosphatidylserine; All groups 60 min, 2/week, 6 months; Individual CG, *n* = 17; Social support; 60 min, 1/week, Individual	8 weeks, 16 weeks, 6 months (PI) MMSE, Orientation, Memory (Verbal and pictorial selective reminding paradigm), Corsi's blockspan, Gollin's incomplete picture test, Verbal fluency, Token test, Reaction time, Alters-Konzentrations-Test: No differences between IG and CG	-	Low (2/10)
Huntley et al. 2017 United Kingdom *n* = 30	AD F 40% 80 years MMSE 26	IG, *n* = 15; Adaptive working memory training on a computer CG, *n* = 15; Non-adaptive, unstructured three-digit span task Both groups 30 min, 2-3/week, 8 weeks; Individual	8 weeks (PI) Digit span (structured), Logical memory task, MMSE, ADAS-Cog: Improvement in IG compared to CG Digit span (random), Spatial span, Paired associates learning task, Executive function (five separate tasks): No differences between groups	++	High (8/10) fMRI: Evidence of change in the functional activity of task-specific cortical networks
Jelcic et al. 2012 Italy *n* = 40	AD F 83% 82 years MMSE 25	IG, *n* = 20; Lexical-semantic stimulation with a wide range of lexical tasks aimed at enhancing semantic verbal processing CG, *n* = 20; Unstructured cognitive stimulation Both groups 60 min, 2/week, 3 months; In groups	3 months (PI), 9 months MMSE, BNT, Verbal Naming Test, Digit Span, Story Delayed Recall: Improvement in IG compared to CG at PI, MMSE remained significantly improved at 9 months Other 9 cognitive outcomes: No differences between groups	++	Moderate (7/10)

Jelcic et al. 2014 Italy *n* = 27	AD F 78% 83 years MMSE 24	IG, *n* = 7; Lexical-semantic stimulation/LSS on verbal semantic processing through a teleconference technology IG2, *n* = 10; Face-to-face LSS intervention CG, *n* = 10; Unstructured cognitive stimulation All groups 60 min, 2/week, 3 months; In groups	3 months (PI) MMSE, Verbal Naming Test, Brief Story Recall (immediate): Improvement in IG and IG2 Digit Span, RAVL (delayed): Improvement in IG2 Other 7 cognitive outcomes: No differences between groups	++	Low (4/10)
Kawashima et al. 2005 Japan *n* = 32	AD F not reported 86 years MMSE 20	IG, *n* = 16; Learning therapy using systematized basic problems in reading and arithmetic; 20 min, 2-6/week, 6 months; Individual CG, *n* = 16; TAU	6 months (PI) FAB: Verbal conceptualization improved in IG MMSE: Remained stable in IG, decline in CG	++	Low (2/10)
Lalanne et al. 2015 France *n* = 33	AD F not reported 72 years MMSE 25	IG, *n* = 16; Cognitive training program for episodic and semantic aspects of autobiographical memory across all life periods CG, *n* = 17; Cognitive training focusing on collective semantic memory Both groups 60 min, 1/week, 6 weeks; Individual	6 weeks (PI), 8 weeks Semantic autobiographical memory, Episodic autobiographical memory: Improvement in IG compared to CG at PI, improvement maintained at 2 weeks after the treatment	++	Low (3/10)
Lee et al. 2013 China *n* = 19	AD F 68% 78 years MMSE 17	IG, *n* = 6; Computer-assisted errorless learning program, guidance when needed IG2, *n* = 6; Therapist-led training program, without a computer CG, *n* = 7; General cognitive stimulation All groups 12-30 min, 2/week, 6 weeks; Individual	6 weeks (PI), 4-5 months MMSE, Hong Kong List Learning Test, Brief Assessment of Prospective Memory-Short Form: No differences between groups	-	Low (4/10) Pilot study
Loewenstein et al. 2004 USA *n* = 44	AD F 41% 77 years MMSE 24	IG, *n* = 25; Cognitive training on face-name associations, orientation, use of a memory book, bill-paying, motor memory and attention; 45 min, 2/week, 12-16 weeks; Individual + In-home training with the assistance of a caregiver CG, *n* = 19; Mental stimulation with computer games and word-finding games; Individual	12-16 weeks (PI), 6 months MMSE, Face-Name Association, Orientation, Making-Change-For-A-Purchase, CPT: Improvement in IG compared to CG at PI, effects maintained at follow-up Informant Questionnaire of the Cognitive Decline: Improvement on memory in IG at PI Other outcomes: No differences between groups	++	Moderate (5/10)

Niu et al. 2010 China *n* = 32	AD F 22% 80 years MMSE 17	IG, *n* = 16; Cognitive stimulation therapy focusing on orientation, verbal fluency, overlapping figures and story learning CG, *n* = 16; Communication exercise on current topics, important life events and psycho-education Both groups 45 min, 2/week, 10 weeks; Individual	10 weeks (PI) MMSE: Improvement in IG compared to CG	+	Moderate (7/10)
Pietilä et al. 2017 Finland *n* = 53	AD F 47% 69 years MMSE 22	IG, *n* = 28; Home-based CCT on attention, memory and problem solving; no fixed session time or frequency, total range 43 min - 144 h, median 20 h in 13 weeks; Individual + Group counseling on CCT; 2 h, 3 sessions; In groups + Psychoeducation; 4 h, 4 sessions; In groups with a caregiver CG, *n* = 25; TAU	14 weeks (PI), 6 months Composite scores of Immediate memory, Delayed memory, Attention and processing speed, and Verbal abilities, Similarities and Block design (WAIS-IV): No differences between groups	-	Moderate (5/10)
Quayhagen et al. 1995 USA *n* = 78	AD F 35% 74 years MDRS ≥90	IG, *n* = 25; In-home dyadic cognitive stimulation program of memory, problem solving and conversation activities executed by a family caregiver; 60 min, 6/week, 12 weeks; Individual CG1, *n* = 28; Passive cognitive stimulation at home CG2, *n* = 25; TAU	12 weeks (PI), 9 months Composite scores of General cognitive functioning, General memory, Nonverbal memory and Fluency: Improvement in IG compared to CG at 12 weeks, return to baseline at 9 months Composite scores of Verbal memory and Problem solving: No differences between groups	++	Low (4/10) Lost to F/U 17%
Quayhagen et al. 2000 USA *n* = 103	AD (70%), vascular or Parkinson dementia F 63% 75 years MDRS > 100	IG, *n* = 21; Home-based cognitive stimulation program for the caregiver-patient dyad focusing on memory, problem solving and conversational fluency, with the caregiver as the intervening agent; 60 min, 5/week, 8 weeks; Individual CG, *n* = 15; TAU	8 weeks (PI) Composite scores of Delayed memory, Verbal fluency, Problem solving: Improvement in IG, no change in CG Composite score of Immediate Memory: No differences between groups	++	Low (3/10)

Tárraga et al. 2006 Spain *n* = 46	AD F 85% 77 years MMSE 22	IG, *n* = 15; Interactive multimedia intervention, exercises in attention, calculation, gnosis, language, memory and orientation; 20 min, 3/week, 24 weeks; Individual + Adult day care using integrated psychostimulation CG1, *n* = 16; Adult day care using integrated psychostimulation; 210 min, daily; In groups CG2, *n* = 12; TAU	12 weeks, 24 weeks (PI) ADAS-Cog: Improvement in IG and CG1 compared to CG2 at 12 weeks, performance level maintained in IG at 24 weeks MMSE: Improvement in IG and CG1 compared to CG2 at 12 weeks, performance level maintained at 24 weeks Syndrom Kurztest, BNT, Verbal fluency, RBMT story recall: No differences between groups	++	Low (4/10)
Trebbastoni et al. 2018 Italy *n* = 140	AD F 60% 75 years MMSE 23	IG, *n* = 54; Cognitive training tasks for memory, attention, language, visuospatial functions and executive functions using paper and pencil and verbal learning exercises; 75 min, 2/week, 24 weeks; In groups CG, *n* = 86; TAU	6 months (PI), 12 months MMSE, Babcock Story recall Test, Verbal phonemic fluency, Corsi Block-tapping Test, Clock Drawing Test: Improvement in IG at PI, decline at 12 months RAVLT, Digit Span, Visual Search Matrix test, BNT, Verbal semantic fluency, Frontal Assessment Battery: No significant differences between groups	++	Moderate (6/10)
Zhuang et al. 2013 China *n* = 43	AD, vascular dementia, or MCI F 76% 83 years MMSE 10	IG, *n* = 19; Human-computer interaction-based cognitive training on picture memorization, sorting, sequencing, drawing and opening a virtual door; 75 min, 3/week, 24 weeks; Individual CG, *n* = 14; TAU (treatment not reported)	24 weeks (PI) Addenbrooke's Cognitive Examination -Revised: No differences between groups	-	Low (3/10) Lost to F/U 23%
Studies on compensating for cognitive impairments					
Amieva et al. 2016 France *n* = 653	AD F 60% 79 years MMSE 22	IG, *n* = 157; Individualized cognitive rehabilitation therapy on personally relevant goals using errorless learning procedure; 90 min, 1/week, 3 months, then 90 min, 1/6 weeks, 21 months; Individual CG, *n* = 154; TAU	3 months (PI), 24 months (PI) ADAS-Cog: No differences between groups	-	High (9/10) Multicenter RCT Lost to F/U 28%
Bourgeois et al. 2016 France *n* = 74	AD F 69% 85 years MMSE 17	IG1, *n* = 15; Errorless learning IG2, *n* = 16; Modeling with spaced retrieval IG3, *n* = 21; Trial and error learning Intervention focused on relearning IADL tasks; All groups 120 min, 2/week, 6 weeks; Individual	7 weeks (PI), 11 weeks MMSE: No differences between groups	-	Moderate (5/10) Lost to F/U 30%

Cahn-Weiner et al. 2003 USA *n* = 34	AD F 58% 77 years MMSE 25	IG, *n* = 17; Memory training program using visualization and categorization techniques CG, *n* = 17; Psychoeducation with no memory training Both groups 45 min, 1/week, 6 weeks; In groups	6 weeks (PI), 14 weeks Hopkins Verbal Learning Test-Revised, Brief Visual Spatial Memory Test-Revised, BNT, COWA, Judgment of Line Orientation, Trail Making Test, Everyday Memory Questionnaire: No differences between groups Enhanced recall of word-lists during the 6-week intervention	-	Low (3/10) Memory training intervention of the ACTIVE study
Clare et al. 2010 United Kingdom *n* = 69	AD (80%), vascular or mixed dementia F 59% 78 years MMSE 23	IG, *n* = 23; Goal-oriented cognitive rehabilitation, training on techniques for learning new information, attention and concentration, and stress management; 60 min, 1/week, 8 weeks; In-home; Individual + Work on goals and strategies with a caregiver between sessions CG1, *n* = 24; Relaxation therapy; 60 min, 1/week, 8 weeks; In-home; Individual CG2, *n* = 22; TAU	8 weeks (PI), 6 months RBMT, Verbal fluency, Test of Everyday Attention: No differences between groups Memory Awareness Rating Scale: Self-ratings of memory performance improved in IG compared to CG2 at 6 months	+	Moderate (7/10) Exploratory fMRI data (n = 19) demonstrate intervention-related activation changes Lost to F/U 19%
Kim 2015 Republic of Korea *n* = 43	AD F 65% 71 years MMSE 23	IG, *n* = 22; Goal-oriented cognitive rehabilitation with practicing orientation, face-name associations, learning memory and sustained attention; 30 min individual + 30 min in groups, 1/week, 8 weeks CG, *n* = 21; Unstructured conversation and health-related videos; 60 min, 1/week, 8 weeks; Individual	8 weeks (PI) Orientation (MMSE): Improvement in IG Memory/Loewenstein Occupational Therapy Cognitive Assessment-geriatric: No differences between groups	+	Low (4/10)
Koltai et al. 2001 USA *n* = 24	AD F not reported 73 years MMSE 24	IG, *n* = 8; Memory and coping program targeting cognitive abilities and emotional adjustment; 60 min, 1/week, 5 weeks; Individual IG2, *n* = 8; Memory and coping program in groups CG, *n* = 8; TAU	5 weeks (PI) MMSE, List-learning/CERAD, Everyday Memory Questionnaire (EMQ): No differences between groups	-	Low (3/10) Pilot study
Kurz et al. 2012 Germany *n* = 201	AD F 44% 74 years MMSE 25	IG, *n* = 100; Training on the use of external memory aids, establishing behavioral routines, activity planning and reminiscence; 60 min, 1/week, 12 weeks; Individual CG, *n* = 101; TAU	3 months (PI), 9 months MMSE, Logical Memory/WMS-R, Trail Making Test, Verbal fluency: No differences between groups	-	High (8/10) Multicenter RCT Lost to F/U 15%

Neely et al. 2009 Sweden *n* = 30	AD or vascular dementia F 50% 75 years MMSE 21	IG, *n* = 10; In-home intervention program focusing on learning strategies in a face-name task and a table setting activity IG2, *n* = 10; Collaborative program involving the caregiver with the same training as for IG Both groups 60 min, 1/week, 8 weeks; Individual CG, *n* = 10; No treatment	8 weeks (PI) Recall of categorisable words: Improvement in IG2 compared to IG and CG Recall of non-categorisable words, Collaborative object recall (random), Collaborative object recall (clustered): No differences between groups	+	Low (2/10)
Tappen and Hain 2014 USA *n* = 68	AD or MCI F 40% 81 years MMSE 25	IG, *n* = 37; In-home cognitive training with caregivers using spaced retrieval paradigm, functional task training and compensatory memory strategies CG, *n* = 31; Organized, sequential life story interviews Both groups 60 min, 2/week, 12 weeks; Individual	12 weeks (PI) Face-Name Association Task, Making change, Balancing Checkbook, Event-related prospective Memory: Improvement in IG compared to CG Fuld Object Memory Evaluation, Event-related prospective Memory (complex), Verbal Fluency, Picture Description Test: No differences between groups	++	Moderate (6/10) Lost to F/U 15%
Voigt-Radloff et al. 2017 The Netherlands *n* = 161	AD, mixed dementia F 57% 77 years MMSE 20	IG, *n* = 81; Errorless learning for relearning activities of daily living CG, *n* = 80; Trial and error learning Both groups 60 min, 1/week, 11 weeks; Individual	16 weeks (PI), 6 months MMSE: No differences between groups	-	Moderate (7/10) Multicenter RCT Lost to F/U 15%

ACTIVE, The Advanced Cognitive Training for Independent and Vital Elderly -study; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; BNT, Boston Naming Test; CCT, Computerized cognitive training; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CG, Control group; COWA, Controlled Oral Word Association (test); CPM, Raven's Colored Progressive Matrices; CPT, Continuous Performance Test; F, Female; FAB, Frontal Assessment Battery; fMRI, Functional Magnetic Resonance Imaging; F/U, Follow-up; IG, Intervention group; MCI, Mild cognitive impairment; MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination; MODA, Milan Overall Dementia Assessment; PI, Post-intervention (assessment); RAVL(T), Rey Auditory Verbal Learning Test; RBMT, The Rivermead Behavioural Memory Test; RCT, Randomized controlled trial; ROCF, Rey–Osterrieth Complex Figure (test); TAU, Treatment as usual; TMT, Trail-Making Test; VOSP, Visual Object and Space Perception (test); WAIS-IV, Wechsler Adult Intelligence Scale, Fourth edition; WMS-R, Wechsler Memory Scale – Revised.

[1]Diagnosis, sex, mean age, and mean cognitive status of the participants.

[2]Evidence of efficacy between the study groups: -, no evidence; +, a positive effect on one outcome; ++, a positive effect on two or more outcomes.

[3]Quality rating of a trial is based on the evaluation criteria presented in Table 5.

2.6.2 Effects on functional abilities

Few studies on CT in dementia have been able to show stability or improvement in ADL/IADL by using an individualized training program. A large multicenter RCT on patients with AD revealed lower functional decline and a six-month delay in institutionalization after individualized cognitive rehabilitation, but failed to show any effect when a restorative CT program was used (Amieva et al., 2016). Clare et al. (2010) and Kim (2015) have shown that individualized cognitive rehabilitation is associated with improved subjective goal performance and satisfaction in patients with dementia. Bourgeois et al. (2016) examined the effectiveness of three different learning methods without a control condition, whereas Voigt-Radloff et al. (2017) compared the effectiveness of two learning methods. Structured relearning improved performance in ADL, and the improvements were maintained for four weeks (Bourgeois et al., 2016), and six months (Voigt-Radloff et al., 2017). The latter two studies were specifically designed to improve ADL functions.

A small study involving a restorative CT program with five cycles of intensive training over one year resulted in stable performance in basic ADL, compared with a decline in a control group (Bergamaschi et al., 2013). An intervention effect on an ADL scale was also detected after a CT program with 10 weekly sessions followed by daily home-based training (Giuli et al., 2016). The findings in several other RCTs on CT in dementia show no beneficial effect on functional abilities (Cahn-Weiner, Malloy, Rebok & Ott, 2003; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Jelcic et al., 2012; Koltai et al., 2001; Kurz et al., 2012; Lee et al., 2013; Loewenstein et al., 2004; Pietilä et al., 2017; Quayhagen et al., 1995, 2000; Tappen & Hain 2014; Tárraga et al., 2006). Details of the trials are shown in Table 3.

2.6.3 Effects on mood and anxiety

Emotional problems of worsened mood and increased anxiety are common in dementia, and impair the psychological well-being of the patients (Finkel, 2001; Lazarus, Newton, Cohler, Lesser & Schweon, 1987). A possible explanation for why cognitive interventions may have an impact on the emotional state of a person might be through enhancing self-efficacy and sense of capability of a person (Bandura, 1994). The effects of CT on mood, anxiety and other neuropsychiatric aspects of dementia have been studied in several RCTs (Amieva et al., 2016; Bergamaschi et al., 2013; Cavallo et al., 2016; Clare et al., 2010; Davis et al., 2001; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Giovagnoli et al., 2017; Giuli et al., 2016; Koltai et al., 2001; Kurz et al., 2012; Lalanne et al., 2015; Lee et al., 2013; Loewenstein et al., 2004; Niu et al., 2010; Pietilä et al., 2017; Zhuang et al., 2013), as shown in Table 3.

To date, evidence of the efficacy of CT as regards mood and anxiety is scarce and based on small studies. Five RCTs revealed a positive effect on mood (De Luca et al., 2016; Lalanne et al., 2015; Lee et al., 2013; Niu et al., 2010; Pietilä et al., 2017), and one study a positive effect on anxiety (Gaitán et al. 2013). Symptoms of anxiety were increased at 12-month follow-up in patients with mild-stage AD or MCI, but significantly less in a CCT-

based intervention group (Gaitán et al., 2013). In contrast, in a small pilot study, a positive effect on mood was reported after therapist-led intervention, but not in a CCT-assisted group (Lee et al., 2013). The results of an equally small study with 20 participants suggested improvement in mood after a web-based rehabilitative program in patients with seemingly mild dementia due to vascular causes (De Luca et al., 2016). We found only one study showing maintenance of emotional benefit after CT combined with home-based CCT and group meetings (Pietilä et al., 2017). Lalanne et al. (2015) observed a positive impact on mood after an individual memory program focusing on autobiographical memories, which may have evoked positive emotions and improved mood among the participants. Positive effects on apathy and depressive symptoms were also reported after another individually conducted CT program (Niu et al., 2010). Based on the available evidence, the effects of CT on mood and anxiety need to be confirmed.

2.6.4 Effects on quality of life

To date, six RCTs have been carried out to evaluate the effects of CT on QoL of patients with dementia (Amieva et al., 2016; Clare et al., 2010; Davis et al., 2001; Kim, 2015; Kurz et al., 2012; Pietilä et al., 2017). As shown in Table 3, in only one small study a favorable change in the QoL of participants was reported, after an 8-week program combining individualized compensatory CT, and CT in groups (Kim, 2015). In addition, a pilot study of 14 participants showed an improvement in QoL after intensive multicomponent training for three months, combining CT with physical exercise and group discussions (Maci et al., 2012). Otherwise, there is little evidence of positive effects of CT on QoL of patients with dementia.

Table 3. Effects of cognitive training on functional and psychological outcomes in patients with dementia.

Trial **Sample size**	**Participants**[1]	**Interventions**	**Assessment time** **Effect on functional/psychological outcomes**	**Efficacy**[2]	**Quality rating**[3] **Comments**
Studies on restorative cognitive training					
Amieva et al. 2016 France *n* = 653	AD F 60% 79 years MMSE 22	IG, *n* = 170; Cognitive training therapy designed to involve various cognitive functions (memory, attention, language, and executive function); 90 min, 1/week, 3 months, then 90 min, 1/6 weeks, 21 months; In groups CG, *n* = 154; TAU	3 months (PI), 24 months (PI) DAD, AGGIR, NPI, Apathy Inventory, Montgomery-Asberg Depression Rating Scale, QoL-AD, Rate of patients alive and without moderately severe/severe dementia, Institutionalization: No differences between groups	-	High (9/10) Multicenter RCT Lost to F/U 28%
Bergamaschi et al. 2013 Italy *n* = 32	AD F not reported 78 years MMSE 21	IG, *n* = 16; Cognitive training in spatial orientation, memory, attention, perception, visual analysis, and recognition of emotional expressions; Five cycles of 120 min, 5/week, 4 weeks; In groups CG, *n* = 16; Daily non-specific cognitive activity at a day centre; In groups	1 year (PI) Index of ADL: Significant difference between groups, stable in IG, decline in CG IADL, Cornell Scale for Depression in Dementia: No differences between groups	+	Moderate (7/10)
Cavallo et al. 2016 Italy *n* = 80	AD F 64% 76 years MMSE 23	IG, *n* = 40; Computerized cognitive training (the software Brainer1) in memory, attention, executive function, and language CG, *n* = 40; Non-specific use of a computer with an interventionist Both groups 30 min, 3/week, 12 weeks; Individual	3 months (PI), 9 months Hospital Anxiety and Depression Scale: No differences between groups	-	High (8/10)
Davis et al. 2001 USA *n* = 37	AD F 57% 71 years MMSE 22	IG, *n* = 19; Cognitive training in spaced retrieval of personal information, face-name associations and mnemonic strategy; 60 min, 1/week, 5 weeks; Individual + In-home attention process training directed by a caregiver; 30 min, 6/week, 5 weeks CG, *n* = 18; Unstructured conversation and psychoeducation; 60 min, 1/week, 5 weeks	5 weeks (PI) GDS, Quality of Life Assessment-Patient: No differences between groups	-	Low (4/10)
De Luca et al. 2016 Italy *n* = 20	Vascular dementia F 50% 78 years MMSE 25	IG, *n* = 10; Web-based rehabilitative program on praxis, attention, visual-spatial memory and verbal fluency; 45 min, 3/week, 8 weeks; Individual CG, *n* = 10; Standard neurorehabilitation	8 weeks (PI) GDS: Improvement in IG, stable in CG ADL, IADL, Bedford Alzheimer Nursing Severity Scale, Brief Psychiatric Rating Scale: No differences between groups	+	Low (3/10)

Gaitán et al. 2013 Spain *n* = 60	AD or MCI F 51% 76 years MMSE 25	IG, *n* = 23; Computer-based cognitive training in attention, memory and executive function; 60 min, 2-3/week, 12 weeks; Individual + Traditional pen-and-paper exercises for 12 months CG, *n* = 16; Traditional pen-and-paper exercises; 60 min, 2-3/week, 12 months; In groups	3 month (PI), 1 year STAI-State: Lower anxiety in IG compared to CG at one year GDS: No differences between groups	+	Moderate (6/10) Lost to F/U 35%
Galante et al. 2007 Italy *n* = 11	AD F not reported 76 years MMSE 23	IG, *n* = 7; Computer-based cognitive intervention covering attention, perception, memory, language and spatial cognition CG, *n* = 4; Semi-structured interviews on current topics and life events Both groups 60 min, 3/week, 4 weeks; Individual	4 weeks (PI), 3 months Basic ADL, IADL, GDS, NPI: No differences between groups	-	Low (4/10) Preliminary data on 11 participants
Giovagnoli et al. 2017 Italy *n* = 50	Probable AD F 61% 74 years MMSE 23	IG, *n* = 13; Cognitive training using verbal and visuospatial stimuli and answering questions CG1, *n* = 13; Active music therapy Both groups 45 min, 2/week, 12 weeks; In groups CG2, *n* = 13; Neuroeducation; 3 sessions, 3 months; In groups	12 weeks (PI), 24 weeks Lubben Social Network Scale: An increase of interpersonal relationships in CG1 and CG2, no change in IG BDI, STAI: Improvement at PI in all groups, stability at 24 weeks, but no differences between groups	-	Moderate (6/10) Lost to F/U 22%
Giuli et al. 2016 Italy *n* = 101	AD F 66% 78 years MMSE 20	IG, *n* = 48; Cognitive training for attention, orientation, episodic and prospective memory and planning (restorative and compensatory approaches); 45 min, 1/week, 10 weeks; Individual + Daily homework with the help and support of a caregiver CG, *n* = 47; TAU including general psychoeducation	10 weeks (PI) Index of ADL, IADL: Stable (ADL) or improved (IADL) in IG compared to CG GDS-30: No differences between groups	++	Moderate (5/10)
Jelcic et al. 2012 Italy *n* = 40	AD F 83% 82 years MMSE 25	IG, *n* = 20; Lexical-semantic stimulation with a wide range of lexical tasks aimed at enhancing semantic verbal processing CG, *n* = 20; Unstructured cognitive stimulation Both groups 60 min, 2/week, 3 months; In groups	3 months (PI), 9 months IADL: No differences between groups	-	Moderate (7/10)

Kawashima et al. 2005 Japan *n* = 32	AD F not reported 86 years MMSE 20	IG, *n* = 16; Learning therapy using systematized basic problems in reading and arithmetic; 20 min, 2-6/week, 6 months; Individual CG, *n* = 16; TAU	6 months (PI) Independence (N Mental State Scale for the Aged): Improved in IG, stable in CG Verbal communication (N Mental State Scale for the Aged): No differences between groups	+	Low (2/10)
Lalanne et al. 2015 France *n* = 33	AD F not reported 72 years MMSE 25	IG, *n* = 16; Cognitive training program for episodic and semantic aspects of autobiographical memory across all life periods CG, *n* = 17; Cognitive training focusing on collective semantic memory Both groups 60 min, 1/week, 6 weeks; Individual	6 weeks (PI), 8 weeks GDS: Improvement in IG compared to CG at PI, maintained at 8 weeks, but no differences between groups at 8 weeks	+	Low (3/10)
Lee et al. 2013 China *n* = 19	AD F 68% 78 years MMSE 17	IG, *n* = 6; Computer-assisted errorless learning program, guidance when needed IG2, *n* = 6; Therapist-led training program, without a computer CG, *n* = 7; General cognitive stimulation All groups 12-30 min, 2/week, 6 weeks; Individual	6 weeks (PI) GDS-Short Form: Improvement in IG2 compared to other groups Modified Barthel Index, IADL: No differences between groups	+	Low (4/10) Pilot study
Loewenstein et al. 2004 USA *n* = 44	AD F 41% 77 years MMSE 24	IG, *n* = 25; Cognitive training on face-name associations, orientation, use of a memory book, bill-paying, motor memory and attention; 45 min, 2/week, 12-16 weeks; Individual + In-home training with the assistance of a caregiver CG, *n* = 19; Mental stimulation with computer games and word-finding games; Individual	12-16 weeks (PI), 6 months Bayer Activities of Daily Living Scale, Revised Memory and Behavior Problems Checklist, Center for Epidemiological Studies-Depression Scale: No differences between groups	-	Moderate (5/10)
Niu et al. 2010 China *n* = 32	AD F 22% 80 years MMSE 17	IG, *n* = 16; Cognitive stimulation therapy focusing on orientation, verbal fluency, overlapping figures and story learning CG, *n* = 16; Communication exercise on current topics, important life events and psycho-education Both groups 45 min, 2/week, 10 weeks; Individual	10 weeks (PI) NPI: Improvement in scores for apathy and depression in IG compared to CG	+	Moderate (7/10)

Pietilä et al. 2017 Finland *n* = 53	AD F 47% 69 years MMSE 22	IG, *n* = 28; Home-based CCT on attention, memory and problem solving; no fixed session time or frequency, total range 43 min - 144 h, median 20 h in 13 weeks; Individual + Group counseling on CCT; 2 h, 3 sessions; In groups + Psychoeducation; 4 h, 4 sessions; In groups with a caregiver CG, *n* = 25; TAU	14 weeks (PI), 6 months The Depression Scale: Improvement in IG at PI, remained stable at 6 months, no change in CG Cornell Scale for Depression in Dementia: Improvement in IG compared to CG at PI QoL-AD, ADCS-ADL: No differences between groups	++	Moderate (5/10)
Quayhagen et al. 1995 USA *n* = 78	AD F 35% 74 years MDRS ≥90	IG, *n* = 25; In-home dyadic cognitive stimulation program of memory, problem solving and conversation activities executed by a family caregiver; 60 min, 6/week, 12 weeks; Individual CG1, *n* = 28; Passive cognitive stimulation at home CG2, *n* = 25; TAU	12 weeks (PI), 9 months Memory and Behavior Problems Checklist: No differences between groups	-	Low (4/10) Lost to F/U 17%
Quayhagen et al. 2000 USA *n* = 103	AD (70%), vascular or Parkinson dementia F 63% 75 years MDRS > 100	IG, *n* = 21; Home-based cognitive stimulation program for the caregiver-patient dyad focusing on memory, problem solving and conversational fluency, with the caregiver as the intervening agent; 60 min, 5/week, 8 weeks; Individual CG, *n* = 15; TAU	8 weeks (PI) Memory and Behavior Problems Checklist: No differences between groups	-	Low (3/10)
Tárraga et al. 2006 Spain *n* = 46	AD F 85% 77 years MMSE 22	IG, *n* = 15; Interactive multimedia intervention, exercises in attention, calculation, gnosis, language, memory and orientation; 20 min, 3/week, 24 weeks; Individual + Adult day care using integrated psychostimulation CG1, *n* = 16; Adult day care using integrated psychostimulation; 210 min, daily; In groups CG2, *n* = 12; TAU	12 weeks, 24 weeks (PI) Rapid Disability Rating Scale-2: No differences between groups	-	Low (4/10)
Zhuang et al. 2013 China *n* = 43	AD, vascular dementia, MCI F 76% 83 years MMSE 10	IG, *n* = 19; Human-computer interaction-based cognitive training on picture memorization, sorting, sequencing, drawing and opening a virtual door; 75 min, 3/week, 24 weeks; Individual CG, *n* = 14; TAU (treatment not reported)	24 weeks (PI) Hamilton Depression Rating Scale: Not reported	-	Low (3/10) Lost to F/U 23%

Studies on compensating for cognitive impairments					
Amieva et al. 2016 France *n* = 653	AD F 60% 79 years MMSE 22	IG, *n* = 157; Individualized cognitive rehabilitation therapy on personally relevant goals using errorless learning procedure; 90 min, 1/week, 3 months, then 90 min, 1/6 weeks, 21 months; Individual CG, *n* = 154; TAU	3 months (PI), 24 months (PI) DAD, AGGIR: Lower functional decline in IG Institutionalization: A six-month delay at two years in IG compared to CG NPI, Apathy Inventory, Montgomery-Asberg Depression Rating Scale, QoL-AD, Rate of patients alive and without moderately severe to severe dementia: No differences between groups	++	High (9/10) Multicenter RCT Lost to F/U 28%
Bourgeois et al. 2016 France *n* = 74	AD F 69% 85 years MMSE 17	IG1, *n* = 15; Errorless learning IG2, *n* = 16; Modeling with spaced retrieval IG3, *n* = 21; Trial and error learning All three interventions focused on relearning IADL tasks; All groups 120 min, 2/week, 6 weeks; Individual	7 weeks (PI), 11 weeks IADL tasks score: Improvement in all groups, maintained at 1 month, no differences between groups NPI: No differences between groups	-/+	Moderate (5/10) Lost to F/U 30% No control condition
Cahn-Weiner et al. 2003 USA *n* = 34	AD F 58% 77 years MMSE 25	IG, *n* = 17; Memory training program using visualization and categorization techniques CG, *n* = 17; Psychoeducation with no memory training Both groups 45 min, 1/week, 6 weeks; In groups	6 weeks (PI), 14 weeks ADL Questionnaire: No differences between groups	-	Low (3/10) Memory training intervention of the ACTIVE study
Clare et al. 2010 United Kingdom *n* = 69	AD (80%), vascular or mixed dementia F 59% 78 years MMSE 23	IG, *n* = 23; Goal-oriented cognitive rehabilitation, training on techniques for learning new information, attention and concentration, and stress management; 60 min, 1/week, 8 weeks; In-home; Individual + Work on goals and strategies with a caregiver between sessions CG1, *n* = 24; Relaxation therapy; 60 min, 1/week, 8 weeks; In-home; Individual CG2, *n* = 22; TAU	8 weeks (PI), 6 months COPM (at PI only): Improvement on perceived goal performance and satisfaction in IG compared to other groups Hospital Anxiety and Depression Scale: Decrease in anxiety in CG2 compared to CG1 at PI Independent Living Scale, QoL-AD: No differences between groups	+	Moderate (7/10) Exploratory fMRI data (*n* = 19) demonstrate intervention-related activation changes Lost to F/U 19%
Kim 2015 Republic of Korea *n* = 43	AD F 65% 71 years MMSE 23	IG, *n* = 22; Goal-oriented cognitive rehabilitation with practicing orientation, face-name associations, learning memory and sustained attention; 30 min individual + 30 min in groups, 1/week, 8 weeks CG, *n* = 21; Unstructured conversation and health-related videos; 60 min, 1/week, 8 weeks; Individual	8 weeks (PI) COPM Satisfaction and Performance ratings, QoL-AD: Improvement in IG, stable in CG Modified Barthel Index: No differences between groups	++	Low (4/10)

Koltai et al. 2001 USA *n* = 24	AD F not reported 73 years MMSE 24	IG, *n* = 8; Memory and coping program targeting cognitive abilities and emotional adjustment; 60 min, 1/week, 5 weeks; Individual IG2, *n* = 8; Memory and coping program in groups CG, *n* = 8; TAU	5 weeks (PI) GDS: No differences between groups	-	Low (3/10)
Kurz et al. 2012 Germany *n* = 201	AD F 44% 74 years MMSE 25	IG, *n* = 100; Training on the use of external memory aids, establishing behavioral routines, activity planning and reminiscence; 60 min, 1/week, 12 weeks; Individual CG, *n* = 101; TAU	3 months (PI), 9 months Bayer-ADL, Aachen Functional Item Inventory, Quality of Life in Dementia, GDS, NPI: No differences between groups Decreased depression in female participants in IG compared to CG at PI and at 9 months	-	High (8/10) Multicenter RCT Lost to F/U 15%
Tappen and Hain 2014 USA *n* = 68	AD or MCI F 40% 81 years MMSE 25	IG, *n* = 37; In-home cognitive training with caregivers using spaced retrieval paradigm, functional task training and compensatory memory strategies CG, *n* = 31; Organized, sequential life story interviews Both groups 60 min, 2/week, 12 weeks; Individual	12 weeks (PI) Bayer-ADL: No differences between groups	-	Moderate (6/10) Lost to F/U 15%
Voigt-Radloff et al. 2017 The Netherlands *n* = 161	AD, mixed dementia F 57% 77 years MMSE 20	IG, *n* = 81; Errorless learning for relearning activities of daily living CG, *n* = 80; Trial and error learning Both groups 60 min, 1/week, 11 weeks; Individual	16 weeks (PI), 6 months Core Elements Method for task performance: Improvement on the trained tasks in both groups, no differences between groups; Improvements maintained for 6 months Interview for Deterioration in Daily Living Activities in Dementia, NPI: Remained stable, no differences between groups	-/+	Moderate (7/10) Multicenter RCT Lost to F/U 15%

ACTIVE, The Advanced Cognitive Training for Independent and Vital Elderly study; AD, Alzheimer's disease; ADCS-ADL, Alzheimer Disease Cooperative Study – Activities of Daily Living; ADL, Activities of Daily Living; AGGIR, Grille d'autonomie Gérontologique Groupes Iso-Ressources; BDI, Beck Depression Inventory; CCT, Computerized cognitive training; CG, Control group; COPM, Canadian Occupational Performance Measure; DAD, Disablement Assessment for dementia (scale); F, Female; fMRI, Functional Magnetic Resonance Imaging; F/U, Follow-up; GDS, Geriatric Depression Scale; IADL, Instrumental Activities of Daily Living; IG, Intervention group; MCI, Mild cognitive impairment; MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PI, Post-intervention (assessment); QoL-AD, Quality of Life – Alzheimer's Disease (scale); RCT, Randomized controlled trial; STAI, State Trait Anxiety Inventory; TAU, Treatment as usual.

[1]Diagnosis, sex, mean age, and mean cognitive status of the participants.

[2]Evidence of efficacy between the study groups: -, no evidence; +, a positive effect on one outcome; ++, a positive effect on two or more outcomes.

[3]Quality rating of a trial is based on the evaluation criteria presented in Table 5.

2.7 Summary of the literature

Dementia is a condition characterized by cognitive, behavioral and functional decline from a person's prior performance level, and progressive inabilities to manage daily activities. The most common type of dementia is AD, and other common late-life disease pathologies include vascular dementia, dementia with Lewy bodies, and mixed dementia (Alzheimer's Association, 2018). The growing prevalence of dementia leads to increasing individual, caregiver, and healthcare burdens, and socioeconomic costs.

New neuroprotective approaches for management of AD are vigorously studied, however, there is no disease-modifying pharmacological treatment for dementia, and the focus has been shifting to non-pharmacological therapies. The main objectives in dementia care are to maintain prevailing cognitive and functional ability, minimize behavioral disturbances, and slow disease progression as much as possible. Cognition is one of the key factors to observe as the disease progresses. During the emergence of non-pharmacological treatments, cognition-focused interventions have diversified, and cognitive stimulation, CT, and cognitive rehabilitation have been used and studied side by side.

Cognitive training is defined as guided practice on a set of standard tasks designed to reflect particular cognitive functions, such as memory, attention, and executive function (Clare & Woods, 2004). It is easy to implement in care settings, fairly inexpensive, and accessible even at home through modern technology. Numerous RCTs have concerned the effects of CT in older persons with dementia. Beneficial effects have been reported in global cognition, training-specific cognition, and sometimes also in ADL functioning, and mood. However, trials on CT in dementia have generally been small, study methodologies limited, interventions highly heterogeneous, and long-term follow-up scarce. Maintenance of training-induced changes, as well as generalized effects on everyday functioning and psychological well-being are important goals, showing the clinical significance of an intervention. The available data is insufficient, and the quality of evidence needs to be improved (Bahar-Fuchs et al., 2013).

To conclude, findings in previous RCTs of the effects of CT in dementia are mixed, and the clinical significance of positive results remains unclear. Cognitively frail older people with dementia are vulnerable. Memory, judgment, and reasoning abilities of the patients deteriorate, emphasizing the need for evidence-based care.

3 Aims of the study

The aims of this study were twofold: to evaluate the current evidence concerning CT in dementia, and to examine the feasibility and effectiveness of a systematic CT program among community-dwelling older adults with dementia compared with controls in a randomized controlled trial, where both the intervention and control groups attended regular adult day care. The specific research questions in Studies I–IV were as follows:

1. What is the evidence from RCTs of the effects of CT in persons with dementia when reviewed systematically? (Study I)
2. Is regular CT feasible among patients with mild to moderate dementia? (Study II)
3. Does systematic CT intervention improve or stabilize cognition, or slow down the decline of cognition in persons with mild to moderate dementia? (Studies III and IV)
4. Do patients with mild to moderate dementia benefit from systematic CT in terms of HRQoL, and psychological well-being? (Studies III and IV)

4 Subjects and methods

The findings of previous RCTs on CT in dementia were systematically reviewed. The review was primarily conducted in 2015 and 2016 (Study I), and completed in 2018. The guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were followed in the review (Moher, Liberati, Tetzlaff & Altman, 2009). However, the protocol was not registered.

The effectiveness of CT intervention among patients with mild to moderate dementia was examined, and the results compared with those in a control group in a FINCOG study, being a single-blinded RCT with two arms (intervention and control groups). Papers II, III and IV report the findings of the FINCOG study. The trial was designed according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (Schulz, Altman & Moher, 2010), and registered at the Australian and New Zealand Clinical Trials Registry with the identifier ACTRN12614000976684 in September 2014.

4.1 Systematic review of randomized controlled trials on cognitive training in dementia

The criteria for a clinical research study to be included in the initial systematic review were as follows: an RCT, participants with clinically diagnosed or probable AD or other established type of dementia, CT used as the primary intervention, or CT included as part of multicomponent rehabilitation, and cognition included as one of the outcome measures, this outcome being assessed using objective tests. CT was defined as repeated practice of cognitively challenging tasks at least once a week for one month, including drill and practice exercises, and/or compensatory strategy training. MEDLINE®, Cochrane Library, DARE and PsycINFO databases were systematically searched for RCTs using terms related to cognitive intervention, AD and dementia: ('cognitive training' OR 'memory training' OR 'cognitive rehabilitation' OR 'cognitive intervention') AND ('Alzheimer*' OR 'dement*' OR 'memory disorder'). Studies concerning only participants with MCI, or elderly people at risk of dementia were excluded.

The initial search was performed in May 2015 and repeated in January and April 2016 (Study I). A supplementary systematic search using the same search method was conducted in April 2018. However, a new exclusion criterion was applied: multimodal interventions including non-cognitive training (e.g. physical exercise) were excluded from the present study in order to increase homogeneity of the types of intervention.

Two independent researchers evaluated the methodological quality of the RCTs using a modified rating system. If differences of opinion emerged during the evaluation, the study was re-evaluated and discussed until a consensus was reached. In the rating system we applied the criteria for randomized intervention trials used by Cochrane and collaborators (Higgins, Altman & Sterne, 2011), criteria for the quality assessment of RCTs referred to as the Delphi list (Verhagen et al., 1998), and the criteria developed by the Evidence-Based

Medicine Working Group (Guyatt, Sackett & Cook, 1993). The 10 criteria in our rating system were as follows:

(1) The inclusion and exclusion criteria are satisfactorily described, and the diagnosis of dementia is based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; APA, 1994), or NINCDS-ADRDA criteria (McKhann et al., 1984).
(2) Groups are comparable at baseline.
(3) The study has sufficient statistical power to detect an effect ($n \geq 25$/group), or an adequate power calculation is presented.
(4) The randomization method is valid (a computerized randomization program or a separate randomization center), and adequately described.
(5) The intervention is adequately described.
(6) The measurements and outcome measures are valid, and well defined.
(7) The group allocation is blinded when assessing the outcomes.
(8) The dropouts are described, and the analyses take them into account.
(9) Intention-to-treat (ITT) analysis is applied.
(10) Appropriate statistical analyses are used (a comparison of outcomes between the groups).

Each criterion was considered to be worth one point. The methodological quality of a research study was considered to be high when it scored 8–10 points, while scores of 5–7 indicated moderate methodological quality, and scores < 5 low quality.

4.2 The Finnish Cognitive Intervention (FINCOG) study

4.2.1 Participants and procedures

Between September 2014 and March 2016 a total of 302 patients with an established dementia diagnosis, who were living at home and attending an adult day-care center twice a week in Helsinki, Finland, were invited to take part in the FINCOG study (Figure 2). They received a letter containing information on the research, voluntary participation and how to get involved. The voluntary patient-caregiver dyads were interviewed via telephone to confirm patients' interest and fulfillment of inclusion criteria.

Altogether, 155 persons (112 women, 43 men) and their main caregivers agreed to participate and were eligible. The inclusion criteria for the trial were: (1) AD or other type of dementia at a very mild, mild, or moderate stage (Clinical Dementia Rating [CDR] scale, 0.5 to 2; Hughes, Berg, Danziger, Coben & Martin, 1982), (2) age ≥ 65 years, (3) Finnish speaking, (4) able to see, hear, read, and write, (5) living at home, and (6) attending an adult day-care center at least twice a week. Exclusion criteria were any terminal disease, severe loss of communicative ability, waiting to be institutionalized, or unavailable proxy.

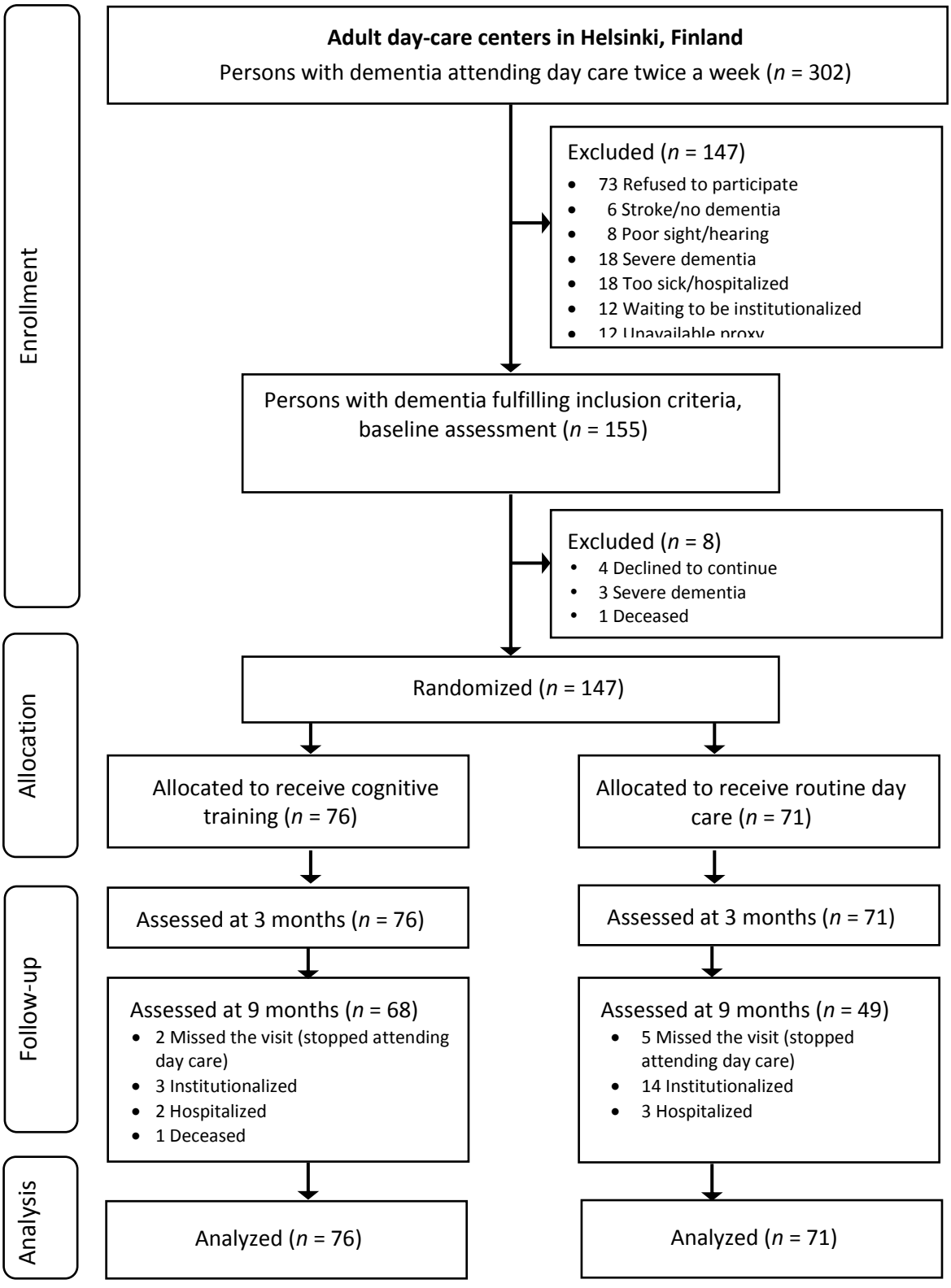

Figure 2. Flowchart of the FINCOG trial.

Figure 2 describes the flowchart of the study. Of the 155 participants assessed thoroughly at baseline, four declined to continue, three persons were found to have severe

dementia in a detailed cognitive assessment, and one person died before randomization. Eventually, there were 147 eligible and voluntary participants in the trial. The dementia diagnoses were confirmed via medical records, which showed that 122 (83%) participants had AD as the primary clinical diagnosis of dementia (NINCDS-ADRDA criteria; McKhann et al., 1984). Other primary diagnoses were evaluated by the study team, using data from medical records: vascular dementia (n = 11), Parkinson's disease or Lewy body dementia (n = 4), or other/unknown type of dementia (n = 10).

4.2.2 Outcome measures

The primary outcome measures of the FINCOG trial were ADAS-Cog scores to assess *general cognitive functioning* (Rosen et al., 1984), and scores in the 15-dimensional (15D) measure of *health-related quality of life* (HRQoL; Sintonen, 2001). The ADAS-Cog instrument, with 11 separate tasks to test memory, language, orientation and praxis has shown sensitivity to cognitive change across various levels of dementia (Mohs, Marin, Green & Davis, 1997). Possible ADAS-Cog scores range from 0 to 70, with higher scores indicating cognitive deterioration. The 15D instrument is a standardized questionnaire including 15 multiple-choice items to measure mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity (Sintonen, 2001). It may be used as a profile measure, or a single index score varying between 0 (poor HRQoL) and 1 (excellent HRQoL). The 15D questionnaire was used in an interview with the participants or their proxies. The 15D questionnaire correlates well with other HRQoL measures (Sintonen, 2001).

Assessment of secondary outcomes included a set of standard neuropsychological tests to measure specific cognitive domains, and a Psychological Well-Being (PWB) scale to assess mood and well-being of the participants (Routasalo, Tilvis, Kautiainen & Pitkälä, 2009). The total score in the Frontal Assessment Battery (FAB) was used as a global measure of *executive functioning* (Dubois, Slachevsky, Litvan & Pillon, 2000). FAB is a short, bedside neuropsychological battery, yielding a maximum score of 18, for assessing patients with degenerative disorders, and indicating executive dysfunction (Dubois et al., 2000). The six FAB tasks explore cognitive and behavioral domains that are thought to be under the control of the frontal networks, such as conceptualization and abstract reasoning, lexical fluency, motor programming, sensitivity to interference, and executive control of action (Dubois et al., 2000). Executive functions that are crucial for intact performance in the FAB instrument are cognitive flexibility and inhibitory control. The Clock-Drawing test (with a range of 0–6 points) of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was used as a measure of planning ability, and verbal fluency was used as an indicator of mental flexibility and cognitive productivity (Sotaniemi et al., 2012). Two separate word-generation tasks were used in this study to give a summarized score of verbal fluency: phonemic (letter S) and semantic (animal) fluency, both within one minute of time.

Time (in seconds) in Part A of the Trail-Making Test (TMT) was used for measuring *selective attention and speed of mental processing* (Reitan, 1955). A verbal Digit Span task from the

Wechsler Memory Scale, Third Edition (WMS-III) was used as a measure of *working memory* capacity involving both forward and backward conditions (Wechsler, 2008). A total score from the two conditions was calculated, yielding a maximum of 32 points. The 12-item Word-recognition task of the ADAS-Cog instrument was used as a measure of *episodic memory* (Rosen et al., 1984). The episodic memory score equals the percentage of correct responses in the task, where 12 studied words are mixed with 12 new words. To assess *reasoning* abilities, *v*erbal concept formation was measured by means of the Similarities subtest, and visuospatial reasoning by means of Block Design, both from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2012).

Additional cognitive measures concerning executive functioning (Victoria Stroop Test), and attention and processing speed (Coding from WAIS-IV) were excluded from the neuropsychological test battery due to excessive complexity. In more than 15% of the cases, both measures had missing data at baseline.

The PWB scale for *psychological well-being* includes six questions about life satisfaction, feeling needed, having plans for the future, having a zest for life, feeling depressed, and suffering from loneliness (Routasalo et al., 2009). These simple questions have been used among older persons with dementia and have been found easy to understand and to answer (Muurinen, Savikko, Soini, Suominen & Pitkälä, 2015; Routasalo et al., 2009). The PWB index score varies between zero (poor well-being) and one (excellent well-being) and can be classified as good (PWB $\geq$ 0.80), moderate (0.80 > PWB $\geq$ 0.40) or poor (PWB < 0.40) (Muurinen et al., 2015). In the FINCOG trial, the PWB responses came from a structured interview with the participant.

In a subgroup of participants, follow-up by means of functional magnetic resonance imaging (fMRI) was intended in order to validate whether changes in brain activity were associated with FINCOG training. A visual working memory task suitable for the study population was designed, and behavioral assessment began. Despite pre-screening, of the first 15 eligible participants prepared for fMRI, only one scan was completed successfully. The participants had various contraindications as regards scanning: a possibility of metal implants (n = 5), cognition- and hearing-based difficulties in following the task protocol (n = 4), and other reasons for low compliance (anxiety, fracture of an arm, refusal). Therefore, fMRI explorations had to be interrupted.

4.2.3 Data collection

The participants were assessed three times during the FINCOG trial: at baseline, and at three and nine months. An experienced neuropsychologist performed all the cognitive assessments, except MMSE. Two study nurses conducted other outcome measures, including MMSE. All the assessors were blinded to group allocation throughout the data collection.

Demographic data and medical history of the participants were collected at baseline. Dementia severity and cognitive status of the participants were assessed using CDR and MMSE, respectively. Medical diagnoses and current medication were confirmed from medical records. The Charlson comorbidity index was calculated to measure the severity of

disease burden (Charlson, Pompei, Ales & MacKenzie, 1987). Self-rated health was evaluated by using a single question "In general, how would you rate your health today" with four answer choices (very good, good, fair or poor). Everyday functioning was measured using the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) questionnaire (Galasko et al., 1997). Independence in daily activities was evaluated using the Personal Care item of the CDR, where a score of 0.5 was evaluated as being fully capable, score 1 as needing prompting, and scores 2 or 3 as requiring assistance (Hughes et al., 1982). The educational level of the participants was classified on the basis of demographic data: less than eight years of education was classified as lower educational level, and eight years or more as higher educational level.

Data collection in the FINCOG trial began in September 2014. The baseline information was collected before randomization, and in the intervention group training started after group allocation. Patients in the intervention group were asked to answer five simple feedback questions after 12 weeks of training. In spring 2016 both recruitment and baseline assessment were completed, and follow-up (outcome measures) was finished in January 2017.

In addition to the above, data on use of health and social services is gathered from hospital and social-service documents and medical records, and death dates from the central registers up to 24 months after baseline.

4.2.4 Randomization

Participants who fulfilled all the inclusion criteria were randomized after the baseline visit into the intervention group (n = 76) or control group (n = 71), using computer-generated random numbers received by telephone from a randomization centre. To enable training in small groups, participants attending day-care centers on the same days were randomized in pairs. However, 18 participants were randomized individually, because no other participants attended a center on the same weekday. To maintain a regular and manageable weekly program, we used the participants' original attendance days throughout the trial.

4.2.5 Cognitive training intervention

A 12-week systematic training program based on paper-and-pencil tasks with cognition as a primary target was designed for the FINCOG trial. The intervention took place twice a week for 45 minutes during adult day care. The main objective of the program was to remediate sub-skills of executive function: attention, working memory, planning, and cognitive flexibility.

The CT program was a relevant modification of cognitive remediation therapy (CRT), which is a form of training-based intervention aimed at improving executive functioning of chronic psychiatric patients (Delahunty & Morice, 1993; Wykes, Huddy, Cellard, McGurk & Czobor, 2011). Cognitive remediation programs, when facilitated by clinicians, are viewed as evidence-based psychological methods in psychiatric rehabilitation (Galletly et al., 2016; Wykes et al., 2011). We adjusted the treatment for our participants by decreasing the

difficulty level of the tasks, reducing the number of sessions from 44 to 24 and increasing the font size of the written tasks. Techniques of repeated practice, errorless learning (i.e. reducing the opportunity to make errors), immediate feedback, scaffolding (i.e. providing strategies when needed, and gradually increasing task complexity), and facilitating planning and self-monitoring were used during the training (Delahunty & Morice, 1993).

Training was tailored according to the participants' cognitive abilities, and therefore implemented either in small groups of 2–4 participants or individually when needed (due to difficulties in concentration or lack of a training pair). To increase the variability of the program, each session included cognitive tasks from four separate categories: visuomotor (e.g. cancellation tasks), perceptual (e.g. searching and counting objects by a simple rule), conceptual (e.g. categorizing words or playing cards), and interactive tasks (e.g. simple card games). Table 4 shows the individual tasks of the program in more detail. Interactive tasks, which encouraged overt conversation, were performed during the last 10–15 minutes of each session to build motivation. Trained psychology students administered CT, with the guidance and supervision of an experienced neuropsychologist.

Both the intervention and control groups received routine treatment at a day-care center twice a week, for six hours each day. Routine treatment included non-specific social (discussions, musical activities, lunch, coffee), physical (light exercise, walking outdoors), and cognitive (orientation, word and number games, reminiscence) activities in groups of 12–16 persons.

Table 4. Tasks designed for cognitive training in the FINCOG trial

Cognitive domain	*Cognitive tasks*
Selective attention	Visual search; Cancellation tasks with alternating objects; Searching for letters and making words; Overlapping figures
Working memory	Counting objects while searching for them; Basic arithmetic; Simple n-back tasks with playing cards; Following verbal instructions; Reading aloud a short text and answering questions
Cognitive flexibility	Cancellation tasks with changing rules; Organizing numbers from the lowest to the highest; Categorizing words and playing cards under a simple rule; Taking turns in interactive word-finding tasks
Planning	Before starting any cognitive task, the participants were asked to stop and think about the best way of completing it

FINCOG, Finnish Cognitive Intervention.

4.2.6 Feedback questionnaire

To assess the feasibility of the CT intervention, a short feedback questionnaire with five simple questions was designed for the participants in the intervention group. The questions were: (1) Were the exercises variable enough? (2) Were the exercises challenging enough? (3) Was the training program too difficult for you? (4) Do you feel that the training was useful

for you? (5) Did the training improve your memory? The options for answering were simply "yes" or "no". The questionnaire was answered anonymously at the end of the last intervention session. The participants were asked to give feedback irrespective of their stage of dementia. The answers were used for the feasibility analyses only, and not to assess the efficacy of CT.

4.2.7 Ethical considerations

The Helsinki University Central Hospital ethics committee approved the FINCOG trial, and the procedures were planned in accordance with the Declaration of Helsinki. Informed consent was obtained from each participant before any study procedures. In cases of a patient's reduced judgment capacity (MMSE score < 20), the closest proxy (spouse or relative) also gave their informed consent.

4.3 Statistical analyses

In the systematic review (Study I) the RCTs were evaluated, and the following data were extracted: sample size, age and sex of participants, dementia diagnosis, MMSE or other dementia rating score, description of the interventions, duration and intensity of the interventions, outcome measures and their time of assessment, and intervention effects. The magnitude of the effect size (ES) of general cognitive functioning was estimated in connection with the methodologically well-conducted trials (i.e. rated as being of high or moderate quality), when possible.

In the FINCOG trial (Studies II–IV), sample-size calculations were based on the primary outcome measure, ADAS-Cog. A four-point change in the ADAS-Cog score was considered as a clinically meaningful difference between intervention and control groups according to previous clinical trials (Kaduszkiewicz, Zimmermann, Beck-Bornholdt & van den Bussche, 2005). A sample size of 64 per group was calculated to ensure 80% power to detect this difference with a standard deviation of 8%, and a type I error rate of 5%. Due to an estimated dropout rate of 20% during follow-up, we aimed to enroll 150 participants. An ITT analysis was applied throughout the trial: all the participants assessed at baseline and at least one of the follow-ups was included in the analyses of changes.

The FINCOG baseline (Study II) statistical analyses included standard descriptive statistics of the participants. The data appear as means with standard deviations, or numbers with percentages. Differences between the intervention and control groups were analyzed by using the chi-square test, Fisher's exact test, the Mann–Whitney *U*-test or Student's *t*-test, as appropriate. The level of significance was 5% in all analyses. In Study II, the categorical feedback data regarding the CT program are presented as percentages.

In Studies III and IV, repeated measurements of primary and secondary outcomes over time were analyzed using a mixed-model approach with appropriate distribution and link function. The normality of variables was assessed on the basis of the Shapiro–Wilk *W* test.

In Study III, the mixed-effects models were applied with an unstructured covariance structure to evaluate changes in ADAS-Cog and 15D data over time. Fixed effects were group, time, and group-time interactions, with age and sex as covariates. Mean changes in separate dimensions of 15D were assessed using paired *t*-tests. Furthermore, responsiveness to the intervention among the participants with mild dementia (CDR 0.5 to 1) was examined. Mean changes in ADAS-Cog scores between the 3-month and baseline values were assessed using analysis of covariance (ANCOVA), with age and sex as covariates.

In Study IV, the standardized response mean (SRM; mean change/standard deviation [SD] of change) of each cognitive measure between the baseline and 3-month assessments was used to compare the responsiveness of different cognitive domains to the intervention. The mean changes between the baseline and 3-month measures were assessed using bootstrap-type ANCOVA, with age, gender, educational level and baseline measure as covariates. Effect sizes (*d*) were calculated by using Cohen's method, where an effect size of 0.20 is considered small, 0.50 moderate, and 0.80 large. Confidence intervals (CIs) for the SRM and effect sizes were obtained by means of bias-corrected bootstrapping (5 000 replications).

A STATA 14.1 (StataCorp LP, College Station, TX, USA) statistical package was used for the analyses.

5 Results

5.1 Systematic review of the effects of cognitive training in dementia (Study I)

A systematic search for research studies conducted in 2015 and in 2016 yielded 58 RCTs for full-text eligibility assessment. In Paper I we reported the results of this initial search, and evaluation of the 31 included trials. The supplementary search in April 2018 resulted in nine new RCTs published between 2016 and 2018. Five RCTs from the initial search combining CT with a non-cognitive intervention technique were excluded from the present study (Figure 3). Altogether, 35 RCTs (n = 2619 participants) on CT in dementia were systematically analyzed.

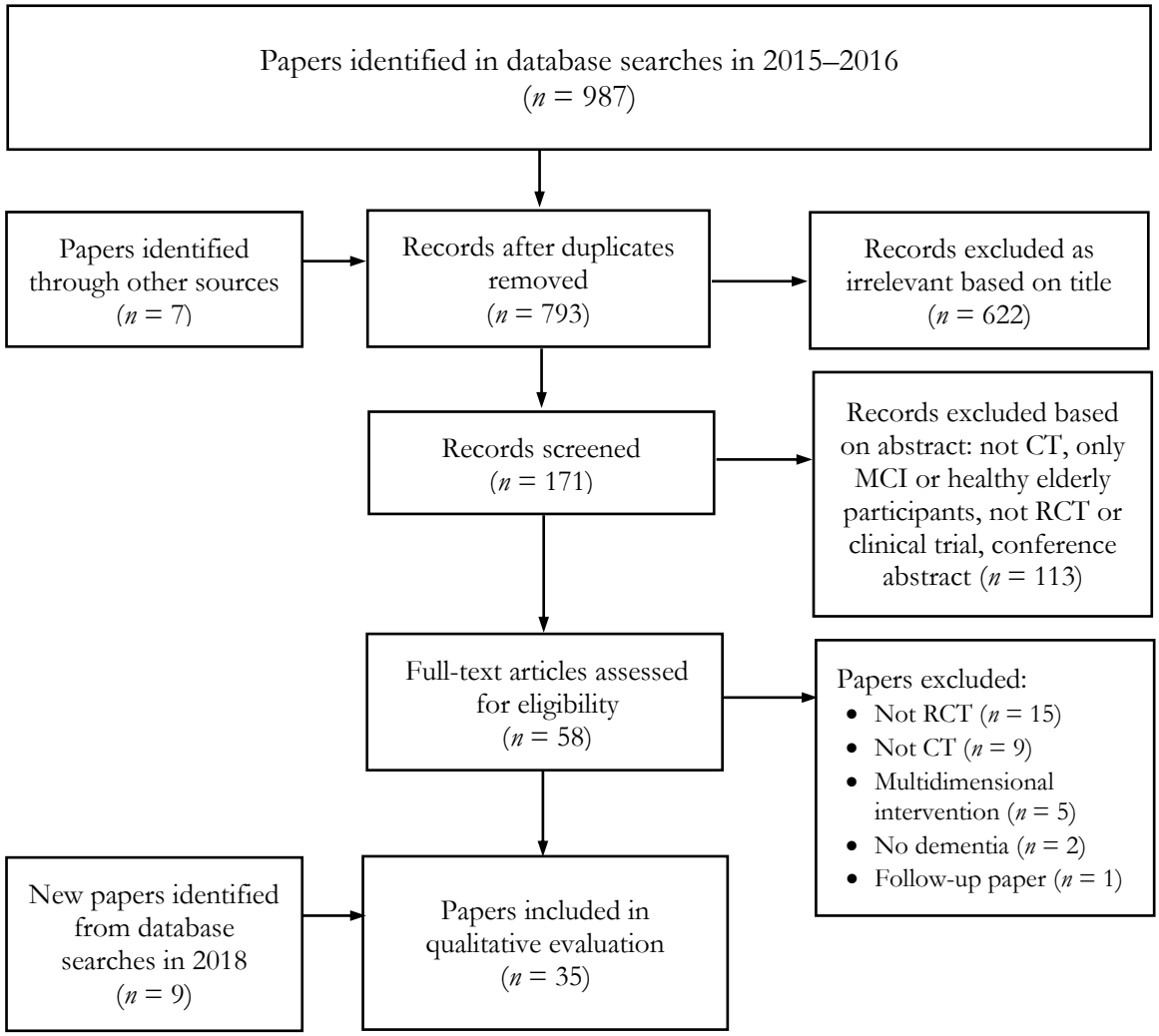

Figure 3. Flowchart of the systematic review.

The number of participants in the 35 RCTs varied from 11 to 653 subjects. Study sizes over 100 participants were found only in six trials (Amieva et al., 2016; Giuli et al., 2016; Quayhagen et al., 2000; Trebbastoni et al., 2018; Kurz et al., 2012; Voigt-Radloff et al., 2017).

5.1.1 Methodological quality of the trials

The methodological quality of the 35 RCTs on the effects of CT in dementia was assessed using a modified rating system (Table 5). Only four of the 35 RCTs were considered as being of high methodological quality, with a total score of eight or nine out of ten (Amieva et al., 2016; Cavallo et al., 2016; Huntley et al., 2017; Kurz et al., 2012), 13 studies were of moderate quality (scores from five to seven), and the remaining 18 studies were evaluated as being of low methodological quality (Table 5). The most often recorded methodological problems were low statistical power, poorly described randomization methods, and non-robust statistical methodology. In addition, the trial drop-outs were inadequately described, and ITT analysis infrequently used.

Table 5. Evaluation of quality criteria fulfillment in RCTs on the effects of CT in dementia. High-quality studies (total score 8–10) are highlighted.

	Criteria[1]										
Study	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	Total
Studies on restorative cognitive training											
Amieva et al. 2016[2]	+	+	+	+	+	+	+	+/-	+	+	9
Beck et al. 1988	+/-	+/-	-	-	-	+/-	-	+	+	-	2
Bergamaschi et al. 2013	+	+	-	+	+	+	+	+/-	+/-	+	7
Breuil et al. 1994	+	+/-	+	-	+	+/-	+	-	-	+/-	4
Cavallo et al. 2016	+	+	+	+	+	+	+	+/-	-	+	8
Davis et al. 2001	+/-	+/-	-	-	+	+	+	+/-	+/-	+	4
De Luca et al. 2016	+/-	+/-	-	-	+	+/-	-	+	+	+/-	3
Gaitán et al. 2013	+	+/-	-	+	+	+	+	+/-	+/-	+	6
Galante et al. 2007	+/-	+/-	-	+	+	+	+	-	+/-	-	4
Giovagnoli et al. 2017	+	+	-	+	+	+	+/-	-	-	+	6
Giuli et al. 2016	+	+/-	+	+	+/-	+	-	-	-	+	5
Heiss et al. 1994	+	+/-	-	-	-	+	-	-	-	+/-	2
Huntley et al. 2017	+	+	-	+	+	+	-	+	+	+	8
Jelcic et al. 2012	+	+	-	+	+	+	+	+/-	+	-	7
Jelcic et al. 2014	+	+/-	-	-	+	+	+	+/-	+/-	-	4
Kawashima et al. 2005	+/-	+	-	-	+	+/-	-	+/-	+/-	-	2
Lalanne et al. 2015	+/-	+	-	-	+	+/-	-	-	+/-	+	3
Lee et al. 2013	+	+/-	-	-	+	+	+	+/-	+/-	-	4
Loewenstein et al. 2004	+	+/-	-	-	+	+	+	+/-	+/-	+	5
Niu et al. 2010	+	+	-	+	+	+/-	+	+	+	-	7
Pietilä et al. 2017	+/-	+	+	+/-	+	+	-	-	-	+	5
Quayhagen et al. 1995	+	+/-	+/-	-	+	+/-	+	-	-	+	4
Quayhagen et al. 2000	+/-	+/-	-	-	+	+/-	+	+/-	+/-	+	3
Trebbastoni et al. 2018	+	+	+	+/-	+	+	+	-	-	+/-	6
Tárraga et al. 2006	+	+/-	-	-	+	+	+	-	-	-	4
Zhuang et al. 2013	+/-	+	-	-	+	+/-	+	+/-	-	-	3
Studies on compensating for cognitive impairments											
Amieva et al. 2016[2]	+	+	+	+	+	+	+	+/-	+	+	9
Bourgeois et al. 2016	+	+	-	-	+	+/-	+	+/-	-	+	5
Cahn-Weiner et al. 2003	+/-	+/-	-	+/-	+	+	+	-	-	+/-	3
Clare et al. 2010	+	+	-	+	+	+	+	+	+/-	+/-	7
Kim 2015	+/-	+	-	-	+	+	+	+/-	+/-	-	4
Koltai et al. 2001	+	+/-	-	-	+	+	+/-	-	+/-	-	3
Kurz et al. 2012	+	+/-	+	+	+	+	+	+	+/-	+	8
Neely et al. 2009	+	-	-	+/-	+	+/-	-	+/-	+/-	+/-	2
Tappen and Hain 2014	+/-	+	+	-	+	+	+	+/-	-	+	6
Voigt-Radloff et al. 2017	+/-	+	+	+	+	+	+	+/-	+/-	+	7

CT, Cognitive training; RCT, Randomized controlled trial; + Criterion fulfilled; +/- Criterion partly fulfilled; - Criterion not fulfilled.

[1]Criteria: (1) Inclusion and exclusion criteria are satisfactorily described, and the diagnosis of dementia is based on DSM-IV (American Psychiatric Association, 2013) or NINCDS-ADRDA criteria (McKhann et al. 1984). (2) Groups are comparable at baseline. (3) The study has sufficient statistical power to detect an effect ($n \geq$ 25/group) or an adequate power calculation is presented. (4) The randomization method is valid (a computerized randomization program or a separate randomization centre) and adequately described. (5) The intervention is adequately described. (6) The measurements and outcome measures are valid and well defined. (7) Group allocation is blinded when assessing the outcomes. (8) Dropouts are described and the analyses take them into account. (9) Intention-to-treat (ITT) analysis is applied. (10) Appropriate statistical analyses are used (comparison is made in relation to outcome variables between the groups).

[2]Amieva et al. (2016) examined the effects of both restorative and compensatory CT with separate intervention groups in the same trial.

5.1.2 Characteristics of the trials

Most of the 35 studies included only, or mainly, patients with AD, while just one study concerned patients with vascular dementia only (DeLuca et al. 2016). The level of participants' cognitive status (i.e. mean MMSE score at baseline) varied from 17 to 26, and their mean age from 67 to 86 years. Female participants predominated in the trials. Table 2 presents the main characteristics of the participants in each RCT.

Twenty-three of the studies concerned CT in an *individual* format (Beck, Heacock, Mercer, Thatcher & Sparkman, 1988; Bourgeois et al., 2016; Cavallo et al., 2016; Clare et al., 2010; Davis et al., 2001; De Luca et al., 2016; Galante et al., 2007; Giuli at al. 2016; Heiss et al., 1994; Huntley et al., 2017; Kawashima et al., 2005; Koltai et al., 2001; Kurz et al., 2012; Lalanne et al., 2015; Lee et al., 2013; Loewenstein et al., 2004; Neely et al., 2009; Niu et al., 2010; Quayhagen et al., 1995, 2000; Tappen & Hain 2014; Voigt-Radloff et al., 2017; Zhuang et al., 2013), eight *in groups* (Amieva et al., 2016; Bergamaschi et al., 2013; Breuil et al., 1994; Cahn-Weiner et al., 2003; Giovagnoli et al., 2017; Jelcic et al., 2012; Jelcic et al., 2014; Trebbastoni et al., 2018), and in four trials *both* individual and group formats were used (Gaitán et al., 2013; Kim 2015; Pietilä et al., 2017; Tárraga et al., 2006).

The most frequently used intervention methods were pen-and-paper exercises and oral tasks, though there were ten studies that involved computerized exercises (Cavallo et al., 2016; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Heiss et al., 1994; Huntley et al., 2017; Lee et al., 2013; Pietilä et al., 2017; Tárraga et al., 2006; Zhuang et al., 2013). Additionally, one study involved teleconference technology (Jelcic et al., 2014). Participants were typically trained in multiple cognitive domains, most often memory, attention, executive function, and language abilities, whereas eight studies were focused on relearning daily activities (Amieva et al., 2016 [individualized cognitive rehabilitation group]; Bourgeois et al., 2016; Clare et al., 2010; Kurz et al., 2012; Loewenstein et al., 2004; Neely et al., 2009; Tappen & Hain 2014; Voigt-Radloff et al., 2017).

In addition to training format and focus, the studies varied considerably in intensity, duration and content of CT programs as well as whether or not an active or passive control group was employed. The total duration of the intervention varied from four weeks (Galante et al., 2007) to one year (Bergamaschi et al., 2013), or in a large-scale RCT, to two years

(Amieva et al., 2013). The frequency of weekly training varied from one session per week to daily training, where a family caregiver was the assistant agent (Davis et al., 2001; Giuli et al., 2016; Pietilä et al., 2017; Quayhagen et al., 1995).

A wide range of outcome measures was used across the studies. The most frequently used single measure was MMSE for global cognitive status (Table 2). In addition to various specific cognitive outcome measures, several functional and psychological outcomes were used (Table 3). Measurements were conducted at baseline before intervention, immediately after the intervention ended, and in less than half of the studies there was a follow-up assessment (Cavallo et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Giovagnoli et al., 2017; Jelcic et al., 2012; Lalanne et al., 2015; Lee et al., 2013; Loewenstein et al., 2004; Pietilä et al., 2017; Quayhagen et al., 1995; Trebbastoni et al., 2018; Bourgeois et al., 2016; Cahn-Weiner et al., 2003; Clare et al., 2010; Kurz et al., 2012; Voigt-Radloff et al., 2017). The follow-up time varied from two weeks (Lalanne et al., 2015) to nine months after the intervention (Gaitán et al., 2013).

5.1.3 Cognitive, functional and psychological outcomes

Two thirds (n = 23) of the 35 RCTs revealed a positive effect in at least one cognitive outcome, whereas half of the studies (n = 17) showed a beneficial effect in more than one cognitive measure (Table 2). A slight improvement in global cognitive status was the most common finding reported (in 15 trials at post-intervention assessment) (Bergamaschi et al., 2013; Breuil et al., 1994; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Giuli et al., 2016; Huntley et al., 2017; Jelcic et al., 2012; Jelcic et al., 2014; Kawashima et al., 2005; Loewenstein et al., 2004; Niu et al., 2010; Quayhagen et al., 1995; Tárraga et al., 2006; Trebbastoni et al., 2018).

In the well-conducted (i.e. high or moderate quality) RCTs the ES as regards general cognitive functioning was large in three trials (Gaitán et al., 2013; Jelcic et al., 2012; Niu et al., 2010), moderate in four trials (Bergamaschi et al., 2013; Cavallo et al., 2016; Huntley et al., 2017; Loewenstein et al., 2004), and small in three trials (Amieva et al., 2016; Giuli et al., 2016; Kurz et al., 2012). In the rest of the high- or moderate-quality studies the ES was not reported, it was not possible to estimate, or global cognition was not used as an outcome measure.

Post-intervention improvement in episodic memory was reported in 11 of the 35 studies (Cavallo et a. 2016; Huntley et al., 2017; Jelcic et al., 2012; Jelcic et al., 2014; Lalanne et al., 2015; Loewenstein et al., 2004; Neely et al., 2009; Quayhagen et al., 1995; Quayhagen et al., 2000; Tappen & Hain 2014; Trebbastoni et al., 2018). Both Cahn-Weiner et al. (2003) and Davis et al. (2001) failed to show an intervention effect in their trained group when compared with controls, but instead were able to show learning gains during the intervention. A positive intervention effect on verbal abilities was reported in nine studies (Bergamaschi, et al., 2013; Cavallo et al., 2016; Giovagnoli et al., 2017; Giuli et al., 2016; Jelcic et al., 2012; Jelcic et al., 2014; Quayhagen et al., 1995; Quayhagen et al., 2000; Trebbastoni et al., 2018), and on working memory in six studies (Bergamaschi et al., 2013; Cavallo et al., 2016; Giuli et

al., 2016; Huntley et al., 2017; Jelcic et al., 2012; Jelcic et al., 2014). In addition, in a few studies positive effects on executive function (Bergamaschi et al., 2013; Cavallo et al., 2016; Gaitán et al., 2013; Kawashima et al., 2005), and on attention were reported (De Luca et al., 2016; Giuli et al., 2016; Loewenstein et al., 2004). Other training-specific cognitive benefits were reported in five studies (Bergamaschi, et al., 2013; Clare et al., 2010; Lalanne et al., 2015; Loewenstein et al., 2004; Kim 2015; Tappen & Hain 2014).

Researchers in five of the nine computerized CT trials found their approach beneficial in terms of different aspects of cognition (Cavallo et al., 2016; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Tárraga et al., 2006). In each of the five interventions a program with three weekly sessions was implemented. In non-effective computerized trials a lower frequency intervention (Heiss et al., 1994; Lee et al., 2013), or self-administered amount of training (Pietilä et al., 2017) was used. In one ineffective study there were older participants with advanced disease (Zhuang et al., 2013).

In twelve trials no effect of CT on cognitive outcomes (intervention vs. control groups) was reported post-intervention (Amieva et al., 2016; Beck et al., 1988; Bourgeois et al., 2016; Cahn-Weiner et al., 2003; Davis et al., 2001; Heiss et al., 1994; Koltai et al., 2001; Kurz et al., 2012; Lee et al., 2013; Pietilä et al., 2017; Voigt-Radloff et al., 2017; Zhuang et al., 2013). None of the large-scale multicenter trials revealed a positive effect on cognition associated with CT (Amieva et al., 2016; Kurz et al., 2012; Voigt-Radloff et al., 2017).

Table 6 summarizes the findings of CT on cognition among patients with dementia in RCTs rated as being of high and moderate methodological quality.

The efficacy of CT on functional and/or psychological outcomes was reported in 14 of the 28 reviewed studies (Amieva et al., 2016; Bergamaschi et al., 2013; Bourgeois et al., 2016; Clare et al., 2010; De Luca et al., 2016; Gaitán et al., 2013; Giuli et al., 2016; Kawashima et al., 2005; Kim 2015; Lalanne et al., 2013; Lee et al., 2013; Niu et al., 2010; Pietilä et al., 2017; Voigt-Radloff et al., 2017) (Table 3). Benefit was typically shown as improved mood (De Luca et al., 2016; Lalanne et al., 2015; Lee et al., 2013; Niu et al., 2010; Pietilä et al., 2017), reduced apathy (Niu et al., 2010) or anxiety (Gaitán et al., 2013), or better ADL functioning (Bergamaschi et al., 2013; Giuli et al., 2016) compared with controls. One of the studies also included data on institutionalization of the patients and progression of AD, and this revealed a six-month delay in institutionalization after individualized cognitive rehabilitation, but not after restorative CT (Amieva et al., 2016). Clare et al., (2010) and Kim (2015) were able to show improvement in goal performance and satisfaction after an individualized CT program. Both Bourgeois et al. (2016) and Voigt-Radloff et al. (2017) found improved performance in trained activities of daily living, but no differences between the treatment groups. Therefore, the learning methods used were found to have similar efficiency, and the improved performance was maintained at follow-up (Bourgeois et al., 2016).

Table 7 summarizes the findings concerning CT and non-cognitive outcomes among patients with dementia in RCTs rated as being of high and moderate methodological quality.

Table 6. Summary of cognitive outcomes in high- and moderate-quality RCTs on CT in dementia.

	Cognitive domains assessed with standard cognitive tests							
Study	Global cognition	Executive function	Attention	Working memory	Episodic memory	Language	Visual perception	Training-specific measures[1]
Studies on restorative cognitive training								
Amieva et al. 2016	0							
Bergamaschi et al. 2013	+	+		+	0		+	
Cavallo et al. 2016	0	0/+		+	0/+	0/+	0	
Gaitán et al. 2013	+	0/+	0	0	0		0	
Giovagnoli et al. 2017		0/+	0	0	0/+	0	0	
Giuli et al. 2016	0/+		+	0/+	0	+		
Huntley et al. 2017	+	0		0/+	0/+			
Jelcic et al. 2012	+	0	0	0/+	0/+	+	0	
Loewenstein et al. 2004	+	0	0/+	0/+	0/+		0	0/+[2]
Niu et al. 2010	+							
Pietilä et al. 2017			0		0	0	0	
Trebbastoni et al. 2018	+	0/+	0	0/+	0/+	0		
Studies on compensating for cognitive impairments								
Amieva et al. 2016	0							
Bourgeois et al. 2016	0							
Clare et al. 2010		0	0		0			+[3]
Kurz et al. 2012	0	0	0		0			
Tappen and Hain 2014					0/+	0		0/+[4]
Voigt-Radloff et al. 2017	0							

CT, Cognitive training; RCT, Randomized controlled trial; +, Significant effect in experimental group; 0/+, Significant effect in some of the outcome measures compared with controls; 0, No difference between intervention and control groups.

[1]A training-specific measure refers to a non-standard task similar to exercises during CT, or to a rating scale.

[2]Recall of face–name associations, Orientation, Change-for-purchase test.

[3]Memory Awareness Rating Scale

[4]Recall and recognition of face–name associations, Calculating change, Balancing checkbook, Event-related prospective memory.

Table 7. Summary of non-cognitive outcomes in high- and moderate-quality RCTs on CT in dementia.

Study	Functional abilities (ADL/IADL)	Depression	Anxiety	Behavioral symptoms	Quality of life	Other outcomes
Studies on restorative cognitive training						
Amieva et al. 2016	0	0		0	0	0
Bergamaschi et al. 2013	0/+	0				
Cavallo et al. 2016		0	0			
Gaitán et al. 2013		0	+			
Giovagnoli et al. 2017		0	0			0
Giuli et al. 2016	+	0				
Jelcic et al. 2012	0					
Loewenstein et al. 2004	0	0		0		0
Niu et al. 2010		+		+		
Pietilä et al. 2017	0	+			0	
Studies on compensating for cognitive impairments						
Amieva et al. 2016	+	0		0	0	0/+[1]
Bourgeois et al. 2016	0/+			0		
Clare et al. 2010	0	0	0		0	+[2]
Kurz et al. 2012	0	0		0	0	
Tappen and Hain 2014	0					
Voigt-Radloff et al. 2017	0/+			0		

ADL, Activities of daily living; CT, Cognitive training; IADL, Instrumental activities of daily living; RCT, Randomized controlled trial; +, Significant effect in experimental group; 0/+, Significant effect in some of the outcome measures compared with controls; 0, No difference between intervention and control groups.

[1] Lower rate of institutionalization

[2] COPM

Finally, long-term sustainability of intervention effects was examined in 16 of the 35 RCTs, with only five studies reporting maintenance of a positive post-intervention effect during follow-up (Cavallo et al., 2016; Galante et al., 2007; Jelcic et al., 2012; Lalanne et al., 2015; Loewenstein et al., 2004). In addition, although Bourgeois et al. (2016), and Voigt-Radloff et al. (2017) did not find differences between their study groups after the ADL relearning period, the post-intervention improvements observed in participants' performances remained stable during follow-up.

The findings in the 17 high- and moderate-quality RCTs on CT in dementia are summarized in Table 8, together with selected characteristics of the participants (age, cognitive status at baseline), and the interventions (intensity and duration of training, method and focus of training).

Table 8. Summary of the findings and trial characteristics of high- and moderate-quality RCTs on CT in dementia.

Study	Efficacy on cognitive outcomes	Generalization of training effect (Yes/No)	Efficacy on non-cognitive outcomes	Stability of effects at follow-up	Mean age of participants	Mean MMSE of participants	Training sessions per week	Duration of training in months	Computerized program (Yes/No)	Individual or group format	Specific training focus (Yes/No)
High-quality trials											
Amieva et al. 2016	0		0		79	22	1	4	No	G	No
Amieva et al. 2016	0		+		79	22	1	4	No	I	Yes
Cavallo et al. 2016	+	No	0	+	76	23	3	3	Yes	I	No
Huntley et al. 2017	+	Yes			80	26	2-3	2	Yes	I	Yes
Kurz et al. 2012	0	No		0	74	25	1	3	No	I	Yes
Moderate-quality trials											
Bergamaschi et al. 2013	+		+		78	21	5	5	No	G	No
Gaitán et al. 2013	+	No	+	0/+	76	25	2-3	3	Yes	I	No
Giovagnoli et al. 2017	0/+	No	0	0/+	74	23	2	3	No	G	No
Giuli et al. 2016	+		+		78	20	1-7	2+	No	I	No
Jelcic et al. 2012	+	Yes	0	0/+	82	25	2	3	No	G	Yes
Loewenstein et al. 2004	+	No	0	+	77	24	2	4	No	I	Yes
Niu et al. 2010	+		+		80	17	2	2+	No	I	No
Pietilä et al. 2017	0	No	+	+	69	22	1-2	3	Yes	I/G	No
Trebbastoni et al. 2018	+	No		0	75	23	2	6	No	G	No
Bourgeois et al. 2016	0		0/+	+	85	17	2	1.5	No	I	Yes
Clare et al. 2010	0/+	No	+		78	23	1+	2	No	I	Yes
Tappen and Hain 2014	0/+	No	0		81	25	2	3	No	I	Yes
Voigt-Radloff et al. 2017	0		0/+	+	77	20	1	3	No	I	Yes

CT, Cognitive training; G, Training in groups; I, Individual training; MMSE, Mini-Mental State Examination; RCT, Randomized controlled trial; +, Significant effect in experimental group; 0/+, Effect in some outcome measures compared with controls; 0, No difference between intervention and control groups.

Based on the findings, the key elements of a beneficial CT intervention in dementia seem to be: (1) specificity of the program (Amieva et al., 2016; Bourgeois et al., 2016; Clare et al., 2010; Huntley et al., 2017; Jelcic et al., 2012; Loewenstein et al., 2004; Tappen and Hain 2014; Voigt-Radloff et al., 2017), (2) frequency of training more than two sessions per week (Bergamaschi et al., 2013; Cavallo et al., 2016; Gaitán et al., 2013; Giuli et al., 2016; Huntley et al., 2017), (3) long duration of training (Amieva et al., 2016; Bergamaschi et al., 2013; Trebbastoni et al., 2018), and (4) computerization of the program (Cavallo et al., 2016; Gaitán et al., 2013; Huntley et al., 2017) (Table 8).

5.2 Characteristics of the participants in the FINCOG study (Studies II–IV)

The mean (SD) age of the 147 participants was 83.1 (5.4) years. A high proportion was female (72%). The educational level of almost 50% of the participants was less than eight years of formal education (Table 8). While 71% of the participants were living alone, only 20% were fully capable of personal care. Functional performance according to the ADCS-ADL inventory was similar in both groups. AD was the primary dementia diagnosis in 83% of the participants. The mean number of eight prescription drugs and a high Charlson index score indicate a high prevalence of comorbid medical conditions in the participants. The most common comorbid conditions were hypertension, hyperlipidemia, osteoarthrosis, cerebrovascular disease and diabetes. More than 80% of the participants were on AD medication, and almost 50% were using anticholinergic drugs. A total of 29% of the participants were using both memantine and anticholinergic drugs.

There were no significant differences in demographic or health-status characteristics between the persons who were randomized to the intervention and control groups (Table 9). Furthermore, the CDR scores and cognitive status assessed by using the MMSE did not differ between the intervention and control groups (Table 9). According to the CDR scores, 10% of the participants were clinically at a very mild stage of dementia, 53% were at a mild stage, and 37% at a moderate stage of dementia. The mean MMSE score of the participants was 20, and the range of MMSE scores was 11–29 in the intervention group, and 12–29 in the control group.

The demographic data of the 147 persons who refused to participate, or who were not eligible at enrollment showed that their mean age (SD) was 82.8 (6.8) years and 71% were female.

Table 9. Demographic and clinical characteristics of the participants in the FINCOG trial.

Characteristics	Intervention group (*n* = 76)	Control group (*n* = 71)	*p*-value
Age, mean (SD)	82.6 (5.5)	83.6 (5.4)	0.24
Female, %	65.8	78.9	0.08
Education < 8 years, %	42.1	50.7	0.30
CDR, %			0.75
0.5	11.8	8.5	
1	52.6	52.1	
2	35.5	39.4	
MMSE, mean (SD)	21.0 (4.3)	19.9 (3.9)	0.12
Dementia diagnosis, %			0.17
AD	76.3	90.1	
Vascular	10.5	4.2	
Parkinson's or Lewy body	3.9	1.4	
Other	9.2	4.2	
Charlson index, mean (SD)	2.7 (1.6)	2.8 (1.9)	0.96
Number of medications, mean (SD)	8.2 (3.2)	7.8 (3.0)	0.34
On AD medication, %	78.9	87.4	0.54
On anticholinergics, %	43.4	52.1	0.29
Living alone, %	71.1	70.4	0.93
Daily activities (CDR, Personal care), %			0.67
Fully capable (0.5)	19.7	21.1	
Needs prompting (1)	40.8	33.8	
Requires assistance (2–3)	39.5	45.0	
ADCS-ADL, mean (SD)	48.7 (14.8) [*n* = 61]	47.2 (16.4) [*n* = 65]	0.63

AD, Alzheimer's Disease; ADCS-ADL, Alzheimer's Disease Cooperative Study – Activities of Daily Living; CDR, Clinical Dementia Rating; FINCOG, Finnish Cognitive Intervention; MMSE, Mini-Mental State Examination; SD, standard deviation.

No statistically significant differences emerged in the primary ADAS-Cog and 15D variables at baseline assessment (Table 10). In general, secondary cognitive measures and psychological well-being were also similar in both groups. Participants in the intervention and control groups differed significantly in a single cognitive measure, the Frontal Assessment Battery. Those in the intervention group scored slightly higher than those in the control group. However, both groups had a mean score below 12, which has been suggested to indicate executive dysfunction (Slachevsky et al., 2004).

Table 10. Mean (SD) cognitive, psychological and quality of life measures at baseline in the FINCOG trial.

Measure	Intervention Group (*n* = 76)	Control Group (*n* = 71)	*p*-value
Global cognition (ADAS-Cog)	21.1 (8.1)	21.8 (8.3)	0.64
Executive functioning			
FAB, total score	11.2 (2.8)	10.2 (2.8)	0.03*
Clock Test (CERAD)	2.8 (1.6)	2.5 (1.4)	0.21
Verbal Fluency, total score	17.7 (8.0)	15.9 (7.8)	0.16
Attention			
TMT, Part A, time (s)	145 (63)	155 (72)	0.37
Working memory			
Digit Span, total score (WMS III)	13.1 (3.2)	12.4 (3.0)	0.14
Episodic memory			
Recognition, % (ADAS-Cog)	67.3 (13.2)	65.1 (13.2)	0.33
Reasoning			
Similarities (WAIS-IV)	15.1 (6.8)	13.3 (6.6)	0.11
Block Design (WAIS-IV)	14.4 (8.2)	14.6 (8.6)	0.89
Psychological well-being (PWB)	0.75 (0.16)	0.76 (0.18)	0.32
Health-related quality of life (15D)	0.743 (0.086)	0.745 (0.081)	0.99

ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; FAB, Frontal Assessment Battery; FINCOG, Finnish Cognitive Intervention; s, Seconds; PWB, Psychological Well-Being (scale); SD, standard deviation; TMT, Trail-Making Test; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WMS III, Wechsler Memory Scale, Third Edition; 15D, 15-dimensional measure of health-related quality of life.

*$p < 0.05$

5.3 Feasibility of cognitive training in dementia (Study II)

Fourteen adult day-care centers in Helsinki participated in the study. Nurses in the centers were interested in the CT intervention, and were helpful in organizing times and places for training sessions over 12-week periods. Participant compliance with training was good, with a mean attendance of 22 out of 24 (92%) sessions. The trainers reported no severe failures of compliance during the CT sessions.

Evaluation of training by means of a short questionnaire (described in Methods [section 4.2.6]) showed favorable feedback from those participating. Of the intervention group, 55 responded to the questionnaire (response rate 72%). Exercises were reported as variable and challenging by 82% of the respondents, and only 5% of the respondents found the program too difficult. A general subjective gain was achieved by 76% of the respondents, and more

than half of the respondents (56%) felt that the training had had a beneficial effect on their memory.

5.4 Effects of cognitive training in home-dwelling patients with dementia

5.4.1 Cognition (Studies III–IV)

Both the intervention and control groups declined in their global cognitive functioning over nine months according to ADAS-Cog scores (Figure 4). However, the two groups did not differ in their changes (p for group = 0.53, time < 0.001, group × time interaction = 0.43, adjusted for age and sex). The total ADAS-Cog score had increased in the intervention group at three months by 0.8 (95% CI -0.2 to 1.8), whereas for the control group the respective change was 1.7 (95% CI 0.6 to 2.7) (p = 0.23, adjusted for age and sex).

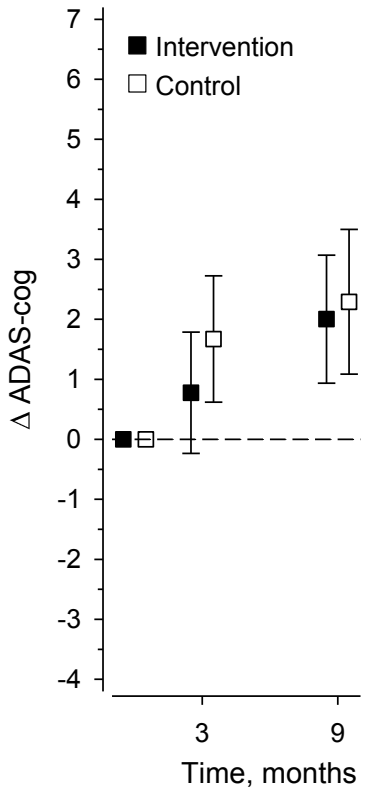

Figure 4. Mean changes in the intervention and control groups in ADAS-Cog scores relative to baseline at 3-month and 9-month assessment points (adjusted for age and sex). An increased ADAS-Cog score indicates cognitive deterioration (the total score range for the scale is 0–70).

Two subgroup analyses were performed to explore whether or not participants at a mild stage of dementia (CDR 0.5 to 1, or MMSE > 20) would benefit from the intervention. For the participants having CDR 0.5 to 1 in the intervention group (n = 49), the increase in the

ADAS-Cog score at three months was 0.6 (95% CI -0.4 to 1.7), whereas in the control group (n = 43) the increase was 1.6 (95% CI 0.4 to 2.7) (p = 0.24, adjusted for age and sex). For the participants in the intervention group with MMSE scores above 20 (n = 45), the increase in the ADAS-Cog score at three months was 0.9 (95% CI -0.3 to 2.0), whereas in the control group (n = 27) the increase was 2.3 (95% CI 0.8 to 3.8) (p = 0.14, adjusted for age and sex).

There were no differences between the intervention and control groups in the mean change in any cognitive domain after the intervention. To compare the different cognitive outcomes with each other, Figure 5 shows the SRMs of cognitive measures in both groups at post-treatment assessment. The actual responses in cognitive measures are shown in Table 11, with respective ESs. The sizes of effects in the cognitive outcomes were generally small. All the comparisons were adjusted for age, sex, educational level and baseline measure.

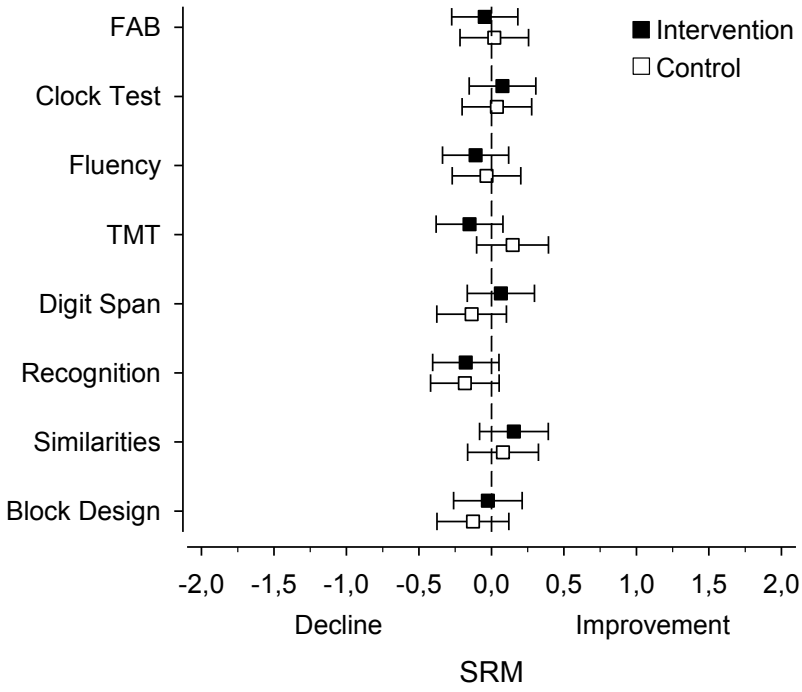

Figure 5. Standardized response means (SRMs) from baseline to 3-month assessment in separate cognitive outcomes in the intervention and control groups (Kallio et al., unpublished results). For the purposes of presentation and comparison of the changes, the standardized response mean (mean change/SD of change) of each measure was applied.

Table 11. Comparisons of mean changes in cognitive measures from baseline to three months in the intervention and control groups (ADAS-Cog: adjusted for age and sex; other measures: adjusted for age, sex, educational level and baseline measure).

Cognitive Measure	Intervention Group Mean Change (95% CI)	Control Group Mean Change (95% CI)	*p*-value	Effect Size (95% CI)
ADAS-Cog	0.8 (-0.2 to 1.8)	1.7 (0.6 - 2.7)	0.23	0.18 (-0.15 to 0.50)
FAB	-0.1 (-0.6 to 0.4)	0.0 (-0.5 to 0.5)	0.96	0.07 (-0.26 to 0.39)
Clock Test	0.12 (-0.23 to 0.47)	0.06 (-0.30 to 0.41)	0.47	-0.04 (-0.37 to 0.29)
Fluency	-0.5 (-1.5 to 0.5)	-0.2 (-1.4 to 1.1)	0.98	0.06 (-0.27 to 0.39)
TMT	7 (-4 to 17)	-6 (-15 to 4)	0.09	-0.29 (-0.64 to 0.05)
Digit Span	0.1 (-0.4 to 0.7)	-0.3 (-0.8 to 0.2)	0.09	-0.20 (-0.55 to 0.15)
Recognition	-1.9 (-4.3 to 0.5)	-2.2 (-5.1 to 0.7)	0.41	-0.03 (-0.36 to 0.30)
Similarities	0.6 (-0.3 to 1.5)	0.4 (-0.7 to 1.5)	0.30	-0.05 (-0.39 to 0.28)
Block Design	-0.2 (-1.7 to 1.3)	-0.8 (-2.2 to 0.7)	0.40	-0.10 (-0.44 to 0.25)

ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive subscale; CI, confidence interval; FAB, Frontal Assessment Battery; TMT, Trail-Making Test.

We further explored whether patients with mild dementia (CDR 0.5–1) would benefit from CT. In subgroup analyses with 49 participants in the intervention group and 43 participants in the control group the responses in several cognitive outcome measures (FAB, Clock Test, Fluency, Digit Span, Recognition, Similarities and Block Design) did not differ between the groups at three months. The mean time in the Trail-Making Test had increased in the intervention group by seven seconds (95% CI -4 to 19), and decreased in the control group by eight seconds (95% CI -19 to 2) at three months ($p = 0.026$, adjusted for age, sex, educational level and baseline measure). The mean time and standard deviation in both the intervention group (mean 137, SD 63) and the control group (mean 143, SD = 60) reflect severe difficulties in TMT performance at baseline, resulting in great variance among participants, which may partly explain this unexpected finding.

The results at three months were in accordance with the results of the primary cognitive outcome measure ADAS-Cog, and therefore no further analyses were conducted at nine months.

5.4.2 Health-related quality of life (Study III)

Both study groups showed a decline from baseline to nine months in their HRQoL according to the 15D instrument (Figure 6). However, the groups did not differ in their changes (p for group = 0.085, time < 0.001, group × time interaction = 0.61, adjusted for age and sex). At three months, the 15D index score had declined from baseline in the intervention group by -0.040 (95% CI -0.058 to -0.021), whereas the respective change in the

control group was -0.037 (95% CI -0.056 to -0.018) (p = 0.82, adjusted for age and sex). Moreover, none of the changes in the separate dimensions of the 15D measure showed significant differences between the intervention and control groups at three months (Figure 7).

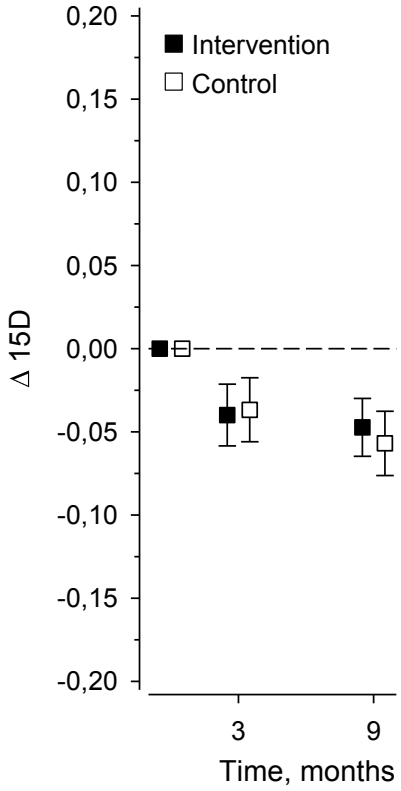

Figure 6. Mean changes in the intervention and control groups in 15D index scores relative to baseline at 3-month and 9-month assessment points (adjusted for age and sex). The 15D score is a summary measure of a 15-dimensional instrument to assess HRQoL, where higher scores indicate better HRQoL. The total score range for the scale is 0–1.

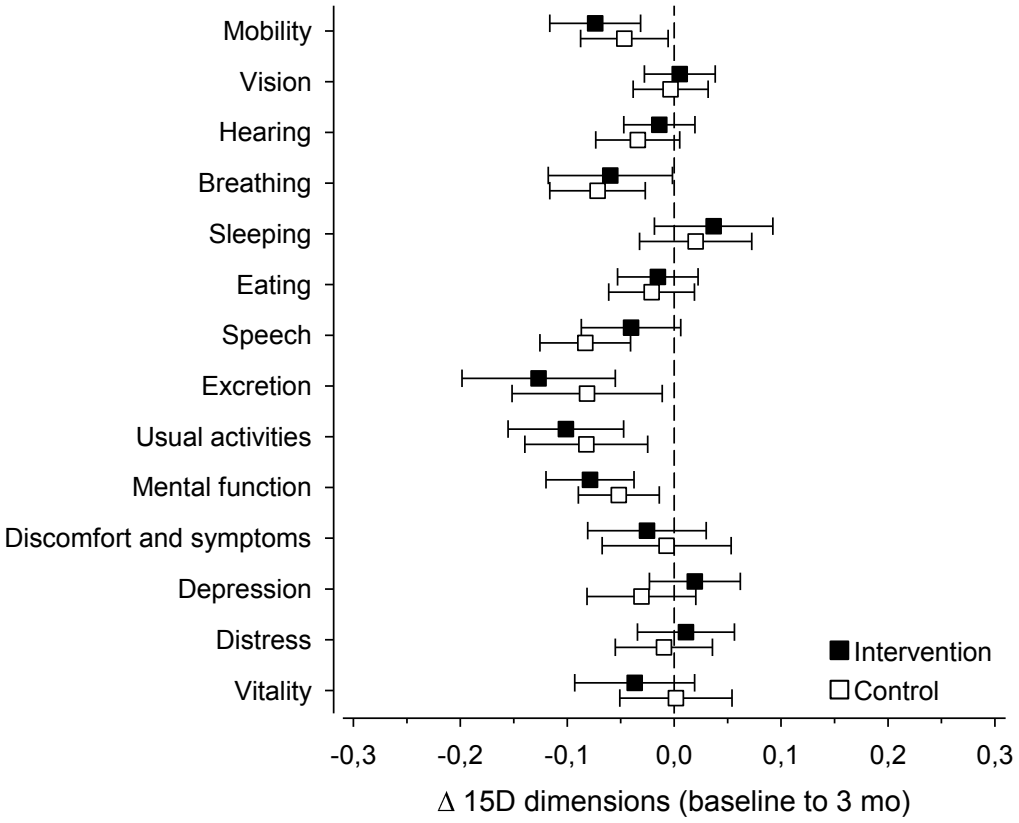

Figure 7. Mean changes in 15D dimensions in the intervention and control groups from baseline to three months (adjusted for age and sex). The range of scores for each dimension is 0–1, higher scores indicating better health-related well-being.

5.4.3 Psychological well-being (Study IV)

According to the PWB score, there were no significant differences in the extent of change in psychological well-being in the study groups after intervention (Figure 8). At three months, the PWB score had declined from baseline by -0.01 (95% CI -0.04 to 0.02) in the intervention group, whereas the respective change in the control group was -0.06 (95% CI -0.10 to -0.02) (p = 0.079, adjusted for age, sex, educational level and baseline measure). At nine months the respective changes were -0.03 (95% CI -0.07 to 0.02) in the intervention group, and 0.01 (95% CI -0.06 to 0.04) in the control group (p = 0.55, adjusted for age, sex, educational level and baseline measure).

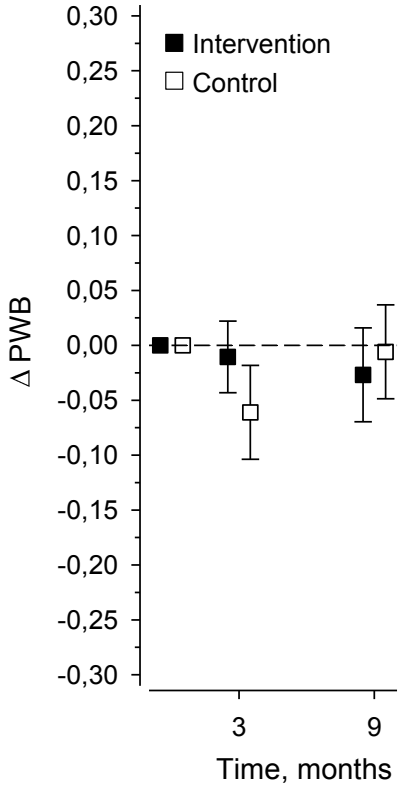

Figure 8. Mean changes in the intervention and control groups in psychological well-being (PWB) relative to baseline at 3-month and 9-month assessment points (adjusted for age and sex; Kallio et al., unpublished results). The range of PWB scores is 0–1, higher scores indicating better well-being.

5.5 Adverse effects of cognitive training in dementia (Studies I–IV)

In the systematic review (Study I), no adverse effects of CT were reported in any of the included trials. Similarly, in the FINCOG trial (Studies II–IV), no adverse events were recorded during the intervention. There were no drop-outs during FINCOG training, and compliance was mostly good. Regular CT in an adult day-care center was safe and meaningful for the participants.

6 Discussion

A systematic review of clinical trials on CT in dementia revealed 35 RCTs concerning the effects of cognition-based training on cognition, functional abilities, mood and quality of life of older adults with predominantly mild or moderate dementia. The results of several studies suggested beneficial effects of CT, but low methodological quality increased the risk of bias in many RCTs, and decreased the grade of evidence. Furthermore, there is little evidence of far-transfer effects, or long-lasting effects of training.

Findings from the FINCOG study, a good-quality RCT concerning the effectiveness of CT on cognition, HRQoL, and psychological well-being in home-dwelling patients with dementia, have not shown any benefit of training. Patients with a mean age of 83 years and established diagnosis of mild to moderate dementia were randomized into an intervention group and a control group. A total of 83% of the participants had a primary diagnosis of AD. The intervention effects were evaluated after a 12-week training program, and follow-up took place months from baseline. CT had no effect on the primary outcomes of global cognition and HRQoL, when compared with those in an active control group. Similarly, secondary cognitive outcomes of executive function, attention, working memory, episodic memory and reasoning, as well as of psychological well-being indicated no effect of training.

6.1 Methodological and theoretical considerations

An RCT is considered to provide the most reliable evidence on the effectiveness of an intervention because the procedures used (Akobeng, 2005). Random allocation of the patients minimizes the risks of confounding factors influencing the results. However, an RCT cannot result in reliable data unless it is planned, conducted, and analyzed in ways that are methodologically sound. The quality of any RCT must be evaluated before its relevance to patient care is considered (Guyatt et al., 1993). The quality depends on study design, prevention of systematic errors, and the use of appropriate analytical techniques (Higgins et al., 2011).

In the present review studies were rated as being of varying methodological quality overall. Four trials were considered to be of high methodological quality, 14 trials were of moderate quality, and 18 trials were of low methodological quality. However, eight of the nine most recent RCTs were on average of better methodological quality, six trials being of moderate and two of high quality. Trials have previously been criticized for low statistical power, incomplete datasets at follow-up, compromising statistical methodology, heterogeneity in training, and also for multiple and non-relevant outcome measures (Bahar-Fuhs et al., 2013; Kurz et al., 2011; Oltra-Cucarella et al., 2016). The same biases were found in the current work. The most common methodological problems were small sample sizes, poorly described randomization methods, and infrequent use of ITT analyses. Study dropouts were rarely included in the analyses. Lack of power and sample calculations were further reasons for a poor quality rating. Outcome measures varied across the studies, and in

many studies multiple tests were utilized to evaluate the efficacy of intervention, thus increasing the risk of false-positive findings. Lastly, the magnitude of treatment effects was rarely reported. However, most investigators sufficiently described their intervention, the assessors evaluating the outcomes were usually blinded to the treatment allocation, and outcome measures were mostly valid.

The heterogeneity of the interventions in the reviewed studies made comparison of their effects difficult. The diversity of CT regarding duration of intervention, number of treatment sessions, intervention focuses and methods, and control conditions did not allow firm conclusions regarding the characteristics of beneficial CT intervention. There was also heterogeneity in the stage of dementia across the study populations, being typically mild, sometimes moderate and a few times even severe. Although specificity of a program, computerization of a program, frequency of training more than twice a week, long duration of training, and combination of CT with other non-pharmacological therapies seemed to be elements that led more often to positive results, no clear indication of the amount of CT, or its content or setting could be detected in the present study.

While RCTs are considered to provide the most reliable evidence of the efficacy of an intervention, the results do not solve the problem of generalization of intervention gains to other settings, such as daily activities (Rabipour & Raz, 2012). In the present review, intervention effects mostly fell into the near-transfer category, and far-transfer effects to other than trained cognitive tasks or domains were rarely reported. Similarly, effective studies in terms of ADL functioning mostly involved an intervention focused on daily activities.

The FINCOG study relied on careful planning and rigorous methodology. It was conducted and reported according to the CONSORT statement (Schulz et al., 2010), and the power calculations were carefully done to ensure the ability of the study to detect a difference between the study groups, if such a difference existed. The exclusion criteria were kept low to enroll a study population that represented well the general home-dwelling dementia population. The trial included participants with different subtypes of dementia, and in mild or moderate stages of dementia to strengthen the generalizability of the results. The participants were living at home, had family caregivers, and they attended adult day care twice a week in the city of Helsinki. Adult day care is offered as part of the social and health-care services to older patients with dementia to sustain their functional independence, support living at home, and to reduce the burden on family caregivers. Thus, the high proportion of participants living alone is well explained by the objectives of adult day care. For the same reason, the mean age (83 years) of the participants was relatively high in the trial. The educational level of the participants was relatively low, which corresponds well with the education of the age cohort in Finland (Official Statistics of Finland, 2014).

Randomization of the 147 participants appeared successful, although stratification by day-care centers and days of attendance was challenging, and some participants had to be randomized and trained individually. Compliance was good in the intervention group, and training well-accepted by the attendees, thus ensuring sufficient practice and enabling real measurements of treatment effects. Training was conducted in small groups of participants, and peer support was a great aid in keeping up training motivation. Moreover, barriers to

participation were low, since day-care attendees are offered free transportation to a day-care center.

The training program in the FINCOG trial was designed to enhance executive functioning of the participants. Executive function encompasses several cognitive skills, such as updating of working memory representations, paying selective attention, inhibitory self-control, and planning (Diamond, 2013; Miyake et al., 2000). Rehabilitation techniques designed to improve such skills are likely to support the functional abilities and quality of life of persons with dementia (Martyr & Clare, 2012). The FINCOG program was based on restorative CT techniques due to deterioration of episodic memory among participants, which substantially restricts the use of compensatory techniques and approaches.

Participants in the control group attended the same adult day care as the participants in the intervention group. Thus, the FINCOG trial concerned the effects of CT over cognitive stimulation activities, which are a regular part of the day-care program. Cognitive stimulation has shown some efficacy as regards cognition in dementia, which may have diluted the difference between the intervention and control arms to some extent (Woods et al., 2012).

The attrition rate of the participants during the 9-month FINCOG study period was 20.4%, which is relatively low and comparable to that in other trials among home-dwelling dementia patients with a long follow-up period (Amieva et al., 2016; Giovagnoli et al., 2017; Kurz et al., 2012; Quayhagen et al., 1995; Voigt-Radloff et al., 2017). There were no dropouts at the 3-month post-intervention assessment.

6.2 Effects of cognitive training on cognition, psychological well-being, and quality of life in dementia

In the present systematic review, two thirds of the 35 RCTs showed a positive effect in at least one cognitive outcome (see Table 2). The use of multiple outcomes increased the risk of false-positive findings in many trials. The most common finding of improved global cognitive functioning at post-intervention assessment was reported in more than half (15 out of 24) of the trials. High- and moderate-quality trials showed a positive effect on global cognition in eight of 14 studies. When reported, the magnitude of effect varied considerably between the studies. Common improvement in global cognitive functioning was an expected finding, since global measures, such as MMSE, give a brief assessment of several cognitive functions, thus detecting and summarizing changes in different cognitive domains.

A beneficial effect in a specific cognitive domain (episodic memory, working memory and language abilities) was occasionally reported, and rarely reported in connection with executive function, attention, visual perception and constructional apraxia. A benefit of training was reported more often after a restorative approach than after compensatory intervention, except where a positive effect was detected in a training-specific task (e.g. Clare et al., 2010; Neely et al., 2009; Tappen & Hain 2014). This would be expected, since the main focus of compensatory approaches is on improving performance in everyday life, and not to remediate cognition *per se* (Clare & Woods, 2004). In general, several trials revealed improvement only in tasks in the same cognitive domain as training, and some in similar

tasks, which is in accordance with the current understanding of brain-training effects (Rabipour & Raz 2012; van Heugten et al., 2016). These results fit under near-transfer effects of training (Zelinski, 2009). Far-transfer effects to domains other than trained cognitive domains were rarely reported. Three small trials involving restorative CT programs with a specific focus resulted in broader benefits for memory (Huntley et al., 2017; Jelcic et al., 2012; 2014) and executive function (Kawashima et al., 2005).

Long-lasting and intense CT seemed to be associated with more frequent cognitive benefits. In a recent study, five intensive one-month cycles of CT resulted in higher scores in global cognition and tests of working memory, and executive and visuospatial function compared with an active control group (Bergamaschi et al., 2013). Multiple cognitive outcomes were used in this study, however, with six out of seven outcomes showing a positive effect after the intervention. Daily CT for 2–6 months at home (Giuli et al., 2016; Loewenstein et al., 2004; Quayhagen et al., 1995, 2000) or in a learning centre (Kawashima et al., 2005) resulted in positive effects on global cognition, episodic memory, executive and language functions, and also in training-specific tasks of face–name associations and working out change for a purchase. Moreover, both Tárraga et al. (2006) and Trebbastoni et al. (2018) continued their programs for approximately six months, and showed improvement in global cognitive functioning.

In most trials the session frequency was twice a week or more. A positive change, most commonly, was detected in global cognition, and in cognitive aspects similar to those in exercises used in the intervention. When the frequency of training was once a week, the only reported benefits were training-specific (Clare et al., 2010; Kim 2015; Lalanne et al., 2015; Neely et al., 2009). In a high-quality multicenter trial, where 653 patients with AD were randomized to receive CT, reminiscence therapy, cognitive rehabilitation, or treatment as usual, the restorative CT program failed to show any cognitive benefit over standard care (Amieva et al., 2016). In this study training included one session a week for the first 12 weeks, and then one session every six weeks for the next 21 months.

A recent systematic literature review and meta-analysis of CT in dementia suggested computer-based cognitive rehabilitation to be more effective than non-computer-based interventions in terms of cognition (García-Casal et al., 2017). In the present review, the studies showing a positive effect after a computerized training program involved frequency of training of three times a week (Cavallo et al., 2016; De Luca et al., 2016; Gaitán et al., 2013; Galante et al., 2007; Tárraga et al., 2006). This is in line with the findings of Lampit et al. (2014), who reviewed CCT in cognitively healthy older adults, and suggested unsupervised at-home training, and training more than three times per week to be ineffective.

An improvement in functional abilities, mood, behavioral symptoms and other non-cognitive outcomes was rarely reported in RCTs on CT in dementia. Overall, 28 RCTs concerned non-cognitive outcomes, and only 14 trials showed partial evidence of benefit after training. Activities of daily living improved especially after programs that were focused on relearning such skills (Bourgeois et al., 2016; Voigt-Radloff et al., 2017), but also after a daily program where one of the training focuses was on planning daily activities at home (Giuli et al., 2016), and after a 1-year restorative CT program (Bergamaschi et al., 2013). In

addition, individualized training programs resulted in lower functional disability (Amieva et al., 2016), and improved goal performance and satisfaction (Clare et al., 2010; Kim 2015). Improvement in mood was most often detected in trials rated as being of low methodological quality. In only two more rigorous RCTs was depression decreased after a CCT program which included regular group meetings (Pietilä et al., 2017), and after an individualized and supportive CT program in a placebo-controlled trial (Niu et al., 2010).

In very few studies has QoL of patients with dementia been measured after a cognition-focused program, and improvement was found only in one small RCT, which used compensatory cognitive training (Kim 2015). One explanation could be the limited sensitivity of functional scales and questionnaires to detect small changes in individual participants (Oltra-Cucarella et al., 2016). QoL, however, is a clinically meaningful outcome that has direct relevance to patients and their caregivers.

Maintenance of the intervention effects at follow-up was studied in less than half of the trials, and observed only in one third of them. To date, evidence of stable intervention effects is weak.

In the present FINCOG trial, no benefit as regards cognition, HRQoL, or psychological well-being was detected after a systematic 12-week CT program conducted in small groups of older patients with mild to moderate dementia, compared with an active control group. The primary cognitive measure ADAS-Cog is sensitive to changes in cognition (Stern et al., 1994), and it did not suffer from floor or ceiling effects among the FINCOG participants. Both the intervention and control groups showed decline in global cognition over time. The result remained the same when a subgroup of patients with only mild dementia was analyzed after the training. The results are consistent with those in a recent large-scale multicenter trial in France, where three different cognition-based intervention groups and a control group included a total of 653 Alzheimer's patients (Amieva et al., 2016). CT consisted of a structured program involving several cognitive functions, such as memory, attention, language, and executive function. Active training took place in small groups for 90 minutes per week for three months, the same weekly amount as in the FINCOG trial. No training-related effects on cognitive or non-cognitive outcomes were detected when compared with usual care (Amieva et al., 2016). Similarly, as an outcome measure of HRQoL, the 15D instrument has shown clinically significant changes in older persons in previous trials (Pitkälä et al., 2008; Suominen et al., 2015). The results in the present trial did not indicate any improvement; rather, post-intervention HRQoL had decreased in both study groups. However, there are some dimensions in 15D that would not be expected to be improved after CT intervention (mobility, vision, hearing, breathing, sleeping and excretion).

In contrast to the present work, several previous studies have shown improvement in separate cognitive domains, many of them training-specific. Recently, after 12 weeks of CCT, a group of early-stage and seemingly purely AD patients showed improvement in various cognitive domains, including tests of executive function and working memory (Cavallo et al., 2016). Exclusion criteria included several common comorbidities of old age, such as other neurological disorders, diabetes and hypertension, and training was administered individually together with a neuropsychologist (Cavallo et al., 2016). In another study, highly intensive

intervention with repeated cycles of CT resulted in increased performance in several areas of cognitive function after one year of training (Bergamaschi et al., 2013). A study conducted in Italy among 48 AD patients revealed improvements in working memory and selective attention after 10 weeks of training in a randomized, but non-blinded trial (Giuli et al., 2016). The training included 10 individual weekly sessions as well as daily homework with the help of a caregiver (Giuli et al., 2016). In a small trial of focused lexical-semantic treatment, patients with mild dementia showed improvement in language abilities, and semantic and episodic memory (Jelcic et al., 2012). Another trial with an equally small sample of mild-dementia patients reported a positive effect on decision-making ability after three months of CCT (Gaitán et al., 2013), and yet another trial on working memory and episodic memory showed a positive effect after eight weeks of focused training (Huntley et al., 2017). All these findings need to be confirmed.

In the present study, psychological well-being was assessed by means of six questions reflecting the participants' mood, zest for life, loneliness and future-orientation. Well-being was moderate at baseline, but contrary to predictions, no change for the better was observed after the intervention. A weak trend at post-intervention assessment suggested a positive change in the PWB scale favoring the intervention group, but the difference between the two groups was not statistically significant.

Only a few previous methodologically sound RCTs have shown a benefit of CT in terms of mood. In Finland, individual home-based CCT focused on attention, memory and problem-solving, combined with regular group meetings resulted in improved mood compared with control conditions, and the difference remained stable six months after the training (Pietilä et al., 2017). Another effective study concerned CT intervention, where priority was given to psychological support over cognitive stimulation (Niu et al., 2010). In addition, studies involving multicomponent intervention for patients with dementia have reported beneficial effects on on mood (Fernández-Calvo et al., 2015; Maci et al., 2012; Olazarán et al., 2004).

The findings in the FINCOG trial are in line with those suggesting that CT might not benefit older adults who already have dementia (Bahar-Fuchs et al., 2013; Hill et al., 2017; Huntley et al., 2015). Then again, it is possible that a restorative CT program of two sessions per week lacked intensity of training. The participants in the present trial were relatively old, with a high number of comorbidities. At the same time, the trial included patients with different types of dementia, and somewhat more advanced disease compared with many studies where participants have been at a mild stage of dementia. However, the results of the FINCOG trial did not change when the main outcomes were analyzed in patients with only mild dementia.

6.3 Clinical implications

Numerous RCTs have been focused on cognitive approaches among patients with established dementia, usually AD. CT is low-cost to implement, accessible through modern computer technology and web-based applications, and unproblematic as regards motivation: CT evokes hope for remediation in older patients with cognitive deterioration. To date, no adverse events have been reported in RCTs on CT in dementia. Similarly, the current FINCOG trial supports the feasibility of CT among older adults with dementia, especially when conducted in small groups of two to four participants during daily programs at an adult day-care center. FINCOG training was well accepted by the participants, adherence to training was good, and many of the participants reported a subjective benefit of training.

Systematic evaluation of the body of current evidence concerning CT in dementia revealed many biases in previous RCTs, decreasing the grade of evidence. Valid conclusions and clinical recommendations should be based on sound evidence. On the basis of the present study, the following remarks can be highlighted: (1) findings on the efficacy of CT in dementia are mixed and inconsistent; (2) due to the wide heterogeneity of intervention characteristics, and trial outcomes that for the most part relate to near-transfer effects of training, no explicit recommendations regarding the type, or content, or amount of training can be made for clinical practice; (3) evidence of clinical significance, i.e. better performance in everyday activities, or maintenance of the intervention effects, is lacking; and (4) the findings in the FINCOG study, a rigorous RCT on CT in dementia, do not support the effectiveness of CT among home-dwelling older patients with mild to moderate dementia. However, on the basis of the current findings, many RCTs have revealed training-specific effects in their study outcomes. These findings suggest that older adults with dementia are able to relearn single functional abilities if a training program is designed according to their current level of cognitive functioning, training focuses on individual goals, and utilizes optimal learning methods (e.g. Amieva et al., 2016; Bourgeois et al., 2016; Voigt-Radloff et al., 2017).

6.4 Strengths and limitations of the study

A rigorous search strategy and broad inclusion criteria for the systematic review resulted in 35 RCTs. The review was designed to answer a specific research question. The precise identification of participants, interventions, outcomes, and effects of an intervention were collected. A flowchart to demonstrate screening of the studies was presented according to PRISMA guidelines (Moher et al., 2009). A descriptive analysis of individual results across the studies was performed, and accompanied with a thorough methodological evaluation by two independent reviewers. However, the review relied on published reports, which may positively skew the results toward a publication bias. Despite careful identification of the interventions used, a wide range of ambiguity remained in classifying the CT programs. Another potential limitation was the variability in the range of disease severity across studies.

Additionally, the considerable variation in duration of the treatments and length of follow-up, if any, limited the evaluation of the long-term effects of the interventions. Consequently, it is unclear whether reported positive effects are sustainable over time.

The FINCOG trial on home-dwelling patients with dementia had several strengths. It was a randomized, single-blinded, controlled trial with separate study personnel performing assessments and interventions. Large trials concerning CT in dementia with high methodological quality are few, as they are laborious to conduct and expensive. With 147 participants randomized in two arms, the study had a larger sample size than most of the previous trials; to our knowledge, there is only one larger RCT conducted on restorative CT (in France) (Amieva et al., 2016). Detailed neuropsychological assessment was performed, and no substantive differences between the groups in terms of demographic characteristics, or cognitive or psychological status before the intervention were found. The outcome assessors were blinded to group allocation. The FINCOG program was carefully planned, and executed to enhance subskills of executive function. Furthermore, it was regular, intensive and well accepted by the participants. Adherence was good in the intervention arm. The FINCOG outcomes of cognitive functioning, psychological well-being, and HRQoL are clinically meaningful and well validated outcomes for older people. Finally, the intervention was planned to be simple enough for easy adoption in adult day care, if it was found to be effective.

The naturalistic nature of the FINCOG study was one of the strengths of the trial, but it may partially explain the negative findings. The exclusion criteria were kept to a minimum. Various dementia diagnoses, both mild and moderate stages of dementia, as well as very old persons with comorbid conditions were allowed. The pragmatic design and heterogeneity of the participants may have diluted the intervention effects. The sample size per group was not large enough to conduct subgroup analysis to identify intervention responders. Moreover, a genuinely adaptive computer-based training program might have had larger training effects than paper-and-pencil exercises with increasing difficulty. The outcome measures of the current study were focused on participants' cognition and quality of life. Ability to perform activities of daily living was assessed at baseline by the caregivers, but this measure had to be excluded from the outcomes of the study because of missing values. Additional information reported by the caregivers might have given a wider perspective on the effectiveness of CT, but unfortunately the data was not available in our study population.

The participants in the FINCOG study were not constrained in engaging in other additional training during the study, but information regarding any home-based cognitive practice was not collected. Two of the 14 day-care centers started their own small-scale cognition-oriented training programs for their attendees during the study, which may have partly attenuated the effects of the FINCOG intervention. Due to occasional implementation, and quite well balanced distribution of this 'extra training', the participants were kept in their randomized research arms.

7 Conclusions

Dementia is an enormous socioeconomic challenge for health and social care systems worldwide, as well as a huge burden to patients and their caregivers. Current pharmacological therapies lack effectiveness, and research efforts to find evidence-based non-pharmacological therapies are in progress. In this thesis, the feasibility and effects of CT in dementia were thoroughly investigated.

A systematic review of RCTs on restorative and compensatory CT in dementia showed contradictory results. Overall, the current body of evidence suggests that CT may lead to observable improvements in global cognitive functioning of older adults with dementia, as well as improvements in enhanced performance in tasks similar to the training exercises. These effects seem to result from relatively long and more intensive training. It also seems that shorter and more individual interventions focusing on a specific aspect of cognitive or everyday functioning may lead to specifically targeted effects. However, there is little evidence of generalization of treatment effects beyond the trained tasks, such as everyday functioning, mood, or quality of life. Moreover, evidence of stability of treatment gains is lacking.

The grade of current evidence is low. Small sample sizes, incomplete data sets, multiple outcomes, and other compromises in study methodology increase the risk of false-positive findings. Furthermore, heterogeneity of training programs in their focus, content, methods, and intensity of training does not allow strong conclusions regarding the effects of CT, or recommendations for clinical practice. Lack of adverse effects suggests, however, that CT is a safe treatment method for older people with dementia.

The present RCT results further suggest that CT is a feasible intervention method in dementia, when conducted in small groups in adult day-care centers. It is well-accepted, and may result in a feeling of subjective benefit. However, the findings of the FINCOG study do not provide support for the effectiveness of CT in patients with dementia. Systematic 12-week CT twice a week for 45 minutes did not result in slower cognitive decline, or stable or increased cognitive functioning, HRQoL, or psychological well-being of the participants. Thus, CT seems to be a feasible but not effective treatment method among older home-dwelling patients with mild to moderate dementia.

8 Future implications

The findings in the current work and the existing literature show that large, rigorously conducted RCTs on CT in dementia are scarce. The results of several small studies have indicated beneficial effects on global cognition and separate training-specific outcomes, and sometimes also on non-cognitive outcomes, such as mood. However, further high-quality studies are needed to confirm these findings. To ensure firm conclusions, careful planning of study design and statistical analyses is recommended, as well as precise definition and description of CT programs in order to enable true comparability across interventions, and clear recommendations for clinical practice.

This doctoral thesis presents evidence that systematic CT is not effective in dementia, when performed in small groups in an adult day-care centers twice a week. Future CT studies should be focused on determination of favorable characteristics of effective treatments. Session frequency more than two times per week, length of a program over three months, programs focusing on a specific goal, as well as computerized and multidimensional programs, all need to be examined more carefully in future studies. Moreover, individualized CT programs may be more effective in terms of cognitive and functional outcomes. Tailoring programs to meet the individual needs and preferences of patients and their caregivers is likely to provide the most beneficial results.

The intention behind using CT in neurodegenerative disorders is to slow disease progression, delay deterioration of cognition, and support independent living. Study designs should accommodate these goals. To date, only one RCT has concerned patient survival in cases without moderately severe to severe dementia, and the findings for the group-based CT were not favorable (Amieva et al., 2016). Future large-scale RCTs with long-term follow-up and clinically relevant outcomes are required to confirm whether CT can improve or stabilize cognitive functioning, delay further disease progression, and help individuals with dementia to manage their everyday activities.

The present findings do not rule out the possibility that CT may be effective in dementia among people of younger age, or with relatively mild cognitive impairment. Determining strategies for dementia prevention is equally important as finding effective treatments for people who already have the condition.

Acknowledgements

The current work was carried out at the Department of General Practice and Primary Health Care, and the Department of Psychology and Logopedics, University of Helsinki, Finland, in 2014–2019. It has been a period of intense learning, not only in the scientific field, but also in personal life. I am grateful to all those who have contributed to the study, and supported me during these years.

First of all, I wish to express my deepest gratitude to my principal supervisor, Professor Kaisu Pitkälä, for her always precise, up-to-date and invaluable guidance. Her admirable ability to set realistic goals and deadlines has kept the project active during these years. I am particularly grateful to her for giving me the opportunity to join her workgroup, and for the trust she placed in me when I started as a researcher. It has been truly inspiring for me to learn about geriatrics and dementia care, as well as intervention study methodology under the guidance of such an expert. Her support has been crucial for the success of this work.

To my supervisor in neuropsychology, Docent Marja Hietanen, I would like to offer my warmest thanks for her expert guidance in neuropsychological methods, and the neuropsychology of neurodegenerative disorders. I have been more than grateful to have her as my supervisor. Moreover, as my superior, Marja has again and again made all the necessary arrangements in the clinic to enable me to continue my research work. I sincerely thank her for that.

I also wish to thank Professor Laura Hokkanen, Head of the Department of Psychology and Logopedics, for her support and practical guidance, especially at the beginning and during the final parts of this project. Her advisory comments and warm encouragement have gently pushed me forward to complete this project.

I would like to express my very great appreciation to my co-authors and co-workers Professor Timo Strandberg, Professor Synnöve Carlson, Virve Vuontela, Helena Soini and Hanna Öhman for sharing their great expertise with me. I am particularly grateful for the assistance given by statistician Hannu Kautiainen. Without his input and expertise I might still be wondering what to do with my research data.

I want to express my warmest thanks to the official reviewers, Professor Roy P. C. Kessels, Radboud University, the Netherlands, and Docent Laura Viikari, University of Turku, for their careful reading and valuable comments on the manuscript, which I think truly improved the final thesis.

I further wish to express my gratitude to Docent Mira Karrasch, Åbo Akademi University, for agreeing to act as the opponent for my dissertation.

I warmly thank Nick Bolton for editing the language of my thesis.

I wish to acknowledge the help and effort provided by study nurses Kaisa Karvinen, Erja Landström and Sirkka Tilvis during the intense period of data collection. I would also like to extend my thanks to the nurses of the adult day-care centers in the City of Helsinki for their help, kindness and flexibility during the trial.

I sincerely thank research assistants Anne Arola, Silja Kervinen, Petra Laamanen, Anita Loikkanen, Tuomas Mansikka, Aino Saarinen, Teemu Valkonen and Tuuli Virolainen for conducting the cognitive training program in the day-care centers. Their willingness to give their time to this project so generously is very much appreciated.

Without the support and understanding of my fantastic colleagues at Helsinki University Hospital this thesis would not have been possible. I feel indebted to you all.

I owe my warmest gratitude to my dear friends. Without their never-ending support, friendship and joy this work would not have been possible. I cannot thank you enough.

I wish to thank my beloved parents Anna-Liisa and Pekka, and my brothers Harri and Tuomas, for their love and support throughout my life and this study. Special thanks go to my father for being my role model in combining scientific research with a true passion for clinical work.

Most of all, Masa and Sanni, you kept my feet firmly on the ground during these years, and reminded me of all those issues in life that ultimately matter.

Finally, I express my warmest thanks to all the patients and their caregivers who participated in the FINCOG trial and made this study possible. The study was financially supported by grants from the Päivikki and Sakari Sohlberg Foundation, the Finnish Brain Foundation, and Helsinki University Hospital (EVO funding).

Helsinki, January 2019

Eeva-Liisa Kallio

References

Aarsland, D., Tandberg, E., Larsen, J. P., & Cummings, J. L. (1996). Frequency of dementia in Parkinson disease. Arch Neurol, 53(6), 538-542.

Akobeng, A. K. (2005). Understanding randomised controlled trials. Archives of Disease in Childhood, 90(8), 840-844.

Albert, M. S. (2011). Changes in cognition. Neurobiol Aging, 32 Suppl 1, S58-63. doi:10.1016/j.neurobiolaging.2011.09.010

Alzheimer's Association. 2018. Alzheimer's Disease Facts and Figures. Alzheimers & Dementia 2018;14(3):367-429.

American Psychiatric Association. (1994). Diagnostic and Statistical Manual of Mental Disorders, Fourth edition; DSM-IV. Washington DC: American Psychiatric Association.

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; DSM-5. Arlington VA: American Psychiatric Association.

Amieva, H., Le Goff, M., Millet, X., Orgogozo, J. M., Peres, K., Barberger-Gateau, P., . . . Dartigues, J. F. (2008). Prodromal Alzheimer's disease: successive emergence of the clinical symptoms. Ann Neurol, 64(5), 492-498. doi:10.1002/ana.21509

Amieva, H., Robert, P. H., Grandoulier, A., Meillon, C., De Rotrou, J., Andrieu, S., . . . Dartigues, J. (2016). Group and individual cognitive therapies in Alzheimer's disease: the ETNA3 randomized trial. International Psychogeriatrics, 28(5), 707-717.

Bahar-Fuchs, A., Clare, L., & Woods, B. (2013). Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database of Systematic Reviews, 2013(6). doi:10.1002/14651858.CD003260.pub2

Ball, K., Berch, D. B., Helmers, K. F., Jobe, B. J., Leveck, M. D., Marsiske, M., . . . Willis, S. L. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. JAMA, 288(18), 2271-2281.

Ball, K., Edwards, J. D., Ross, L. A., & McGwin, J. G. (2010). Cognitive Training Decreases Motor Vehicle Collision Involvement of Older Drivers. Journal of the American Geriatrics Society, 58(11), 2107-2113. doi:10.1111/j.1532-5415.2010.03138.x

Bandura, A. (1994). Self-efficacy. In Ramachaudran V.S. (Ed.) Encyclopedia of human behavior (Vol. 4, pp. 71-81). New York: Academic Press.

Bang, J., Spina, S., & Miller, B. L. (2015). Frontotemporal dementia. The Lancet, 386(10004), 1672-1682. doi:https://doi.org/10.1016/S0140-6736(15)00461-4

Barban, F., Annicchiarico, R., Pantelopoulos, S., Federici, A., Perri, R., Fadda, L., . . . Caltagirone, C. (2016). Protecting cognition from aging and Alzheimer's disease: a computerized cognitive training combined with reminiscence therapy. International Journal of Geriatric Psychiatry, 31(4), 340-348.

Barban, F., Mancini, M., Cercignani, M., Adriano, F., Perri, R., Annicchiarico, R., . . . Bozzali, M. (2017). A Pilot Study on Brain Plasticity of Functional Connectivity Modulated by Cognitive Training in Mild Alzheimer's Disease and Mild Cognitive Impairment. Brain Sciences, 7(5), 50. http://doi.org/10.3390/brainsci7050050

Barker, W. W., Luis, C. A., Kashuba, A., Luis, M., Harwood, D. G., Loewenstein, D., . . . Duara, R. (2002). Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis Assoc Disord, 16(4), 203-212.

Beck, C., Heacock, P., Mercer, S., Thatcher, R., & Sparkman, C. (1988). The impact of cognitive skills remediation training on persons with Alzheimer's disease or mixed dementia. J of Geriatr Psychiatry, 21(1), 73-88.

Belleville, S., Clement, F., Mellah, S., Gilbert, B., Fontaine, F., & Gauthier, S. (2011). Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain, 134(Pt 6), 1623-1634. doi:10.1093/brain/awr037

Bergamaschi, S., Arcara, G., Calza, A., Villani, D., Orgeta, V., & Mondini, S. (2013). One-year repeated cycles of cognitive training (CT) for Alzheimer's disease. Aging Clinical and Experimental Research, 25(4), 421-426.

Birks, J., Grimley Evans, J., Iakovidou, V., Tsolaki, M., & Holt, F. E. (2009). Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev(2), Cd001191. doi:10.1002/14651858.CD001191.pub2

Birks, J. S., & Harvey, R. J. (2018). Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev, 6, Cd001190. doi:10.1002/14651858.CD001190.pub3

Boller, F., & Forbes, M. M. (1998). History of dementia and dementia in history: An overview. Journal of the Neurological Sciences, 158(2), 125-133. doi:https://doi.org/10.1016/S0022-510X(98)00128-2

Bottino, C. M., Carvalho, I. A., Alvarez, A. M., Avila, R., Zukauskas, P. R., Bustamante, S. E., . . . Câmargo, C. H. (2005). Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. Clin Rehabil, 19, 861-869.

Bourgeois, J., Laye, M., Lemaire, J., Leone, E., Deudon, A., Darmon, N., . . . Robert, P. (2016). Relearning of Activities of Daily Living: A Comparison of the Effectiveness of Three Learning Methods in Patients with Dementia of the Alzheimer Type. J Nutr Health Aging, 20(1), 48-55. doi:10.1007/s12603-015-0597-6

Boyke, J., Driemeyer, J., Gaser, C., Buchel, C., & May, A. (2008). Training-induced brain structure changes in the elderly. J Neurosci, 28(28), 7031-7035. doi:10.1523/jneurosci.0742-08.2008

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol, 82(4), 239-259.

Breuil, V., de Rotrou, J., Forette, F., Tortrat, D., Ganansia-Ganem, A., Frambourt, A., . . . Boller, F. (1994). Cognitive stimulation of patients with dementia: preliminary results. Int J Geriatr Psychiatry, 9, 211-217.

Buchman, A. S., Schneider, J. A., Leurgans, S., & Bennett, D. A. (2008). Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology, 71(7), 499-504. doi:10.1212/01.wnl.0000324864.81179.6a

Butler, M., McCreedy, E., Nelson, V. A., Desai, P., Ratner, E., Fink, H. A., . . . Kane, R. L. (2018). Does cognitive training prevent cognitive decline?: A systematic review. Annals of Internal Medicine, 168(1), 63-68. doi:10.7326/M17-1531

Bäckman, L., Small, B. J., & Fratiglioni, L. (2001). Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain, 124(Pt 1), 96-102.

Cahn-Weiner, D. A., Malloy, P. F., Rebok, G. W., & Ott, B. R. (2003). Results of a randomized placebo-controlled study of memory training for mildly impaired Alzheimer's disease patients. Appl Neuropsychol, 10, 215-223.

Caselli, R. J., Beach, T. G., Knopman, D. S., & Graff-Radford, N. R. (2017). Alzheimer's Disease: Scientific Breakthroughs and Translational Challenges. Mayo Clinic proceedings, 92(6), 978-994. doi:10.1016/j.mayocp.2017.02.011

Cavallo, M., Hunter, E., van der Hiele, K., & Angilletta, C. (2016). Computerized structured cognitive training in patients affected by early-stage Alzheimer's disease is feasible and effective: A randomized controlled study. Archives of Clinical Neuropsychology, 31, 868-876.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Chronic Diseases, 40(5), 373-383.

Choi, J., & Twamley, E. W. (2013). Cognitive rehabilitation therapies for Alzheimer's disease: A review of methods to improve treatment engagement and self-efficacy. Neuropsychology Review, 23, 48-62. doi:10.1007/s11065-013-9227-4

Cicerone, K. D., Langenbahn, D. M., Braden, C., Malec, J. F., Kalmar, K., Fraas, M., . . . Ashman, T. (2011). Evidence-Based Cognitive Rehabilitation: Updated Review of the Literature From 2003 Through 2008. Archives of Physical Medicine and Rehabilitation, 92(4), 519-530. doi:10.1016/j.apmr.2010.11.015

Clare, L., Linden, D. E., Woods, R. T., Whitaker, R., Evans, S. J., Parkinson, C. H., . . . Rugg, M. D. (2010). Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer disease: A single-blind randomized controlled trial of clinical efficacy. Am J Geriatr Psychiatry, 18, 928-939.

Clare, L., & Woods, R. T. (2004). Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. Neuropsychological Rehabilitation, 14, 385-401. doi:10.1080/09602010443000074

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci, 14(2), 125-130. doi:10.1111/1467-9280.t01-1-01430

Cummings, J. L. (2005). Behavioral and neuropsychiatric outcomes in Alzheimer's disease. CNS Spectr, 10(11 Suppl 18), 22-25.

Davis, R. N., Massman, P. J., & Doody, R. S. (2001). Cognitive intervention in Alzheimer disease: A randomized placebo-controlled study. Alzheimer Dis Assoc Disord, 15, 1-9.

de Bruijn, R. F., Bos, M. J., Portegies, M. L., Hofman, A., Franco, O. H., Koudstaal, P. J., & Ikram, M. A. (2015). The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. BMC Med, 13, 132. doi:10.1186/s12916-015-0377-5

De Luca, R., Bramanti, A., De Cola, M. C., Leonardi, S., Torrisi, M., Aragona, B., . . . Calabro, R. S. (2016). Cognitive training for patients with dementia living in a sicilian nursing home: a novel web-based approach. Neurol Sci, 37(10), 1685-1691. doi:10.1007/s10072-016-2659-x

Delahunty, A., & Morice, R. (1993). Toiminnanohjauksen ohjelma [Frontal/Executive Program. A Manual for Neurocognitive Rehabilitation for Patients with Chronic Schizophrenia]. (L. Luoma, Trans.). Albury, NSW: Mental Health Unit, South West health Districts.

Diamond, A. (2013). Executive functions. Annual Review of Psychology, 64, 135-168. doi:10.1146/annurev-psych-113011-143750

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000). The FAB: A frontal assessment battery at bedside. Neurology, 55, 1621-1626.

Eloniemi-Sulkava, U., Saarenheimo, M., Laakkonen, M. L., Pietila, M., Savikko, N., Kautiainen, H., . . . Pitkala, K. H. (2009). Family care as collaboration: effectiveness of a multicomponent support program for elderly couples with dementia. Randomized controlled intervention study. J Am Geriatr Soc, 57(12), 2200-2208. doi:10.1111/j.1532-5415.2009.02564.x

Emre, M., Aarsland, D., Brown, R., Burn, D. J., Duyckaerts, C., Mizuno, Y., . . . Dubois, B. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord, 22(12), 1689-1707; quiz 1837. doi:10.1002/mds.21507

Fernández-Calvo, B., Contador, I., Ramos, F., Olazarán, J., Mograbi, D. C., & Morris, R. G. (2015). Effect of unawareness on rehabilitation outcome in a randomised controlled trial of multicomponent intervention for patients with mild Alzheimer's disease. Neuropsychological Rehabilitation, 25(3), 448-477.

Finkel, S. I. (2001). Behavioral and psychological symptoms of dementia: a current focus for clinicians, researchers, and caregivers. J Clin Psychiatry, 62 Suppl 21, 3-6.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). 'Mini-mental state' a practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research, 12, 189-198.

Fratiglioni, L., Wang, H. X., Ericsson, K., Maytan, M., & Winblad, B. (2000). Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet, 355(9212), 1315-1319. doi:10.1016/s0140-6736(00)02113-9

Förstl, H., & Kurz, A. (1999). Clinical features of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci, 249(6), 288-290.

Gaitán, A., Garolera, M., Cerulla, N., Chico, G., Rodriguez-Querol, M., & Canela-Soler, J. (2013). Efficacy of an adjunctive computer-based cognitive training program in amnestic mild cognitive impairment and Alzheimer's disease: a single-blind, randomized clinical trial. International Journal of Geriatric Psychiatry, 28(1), 91-99.

Galante, E., Venturini, G., & Fiaccadori, C. (2007). Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. G Ital Med Lav Ergon, 29(3 Suppl B), B26-32.

Galasko, D., Bennett, D., Sano, M., Ernesto, C., Thomas, R., Grundman, M., & Ferris, S. (1997). An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. Alz Dis Assoc Dis, 11, S33-S39.

Galletly, C., Castle, D., Dark, F., Humberstone, V., Jablensky, A., Killackey, E., . . . Tran, N. (2016). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. The Australian and New Zealand Journal of Psychiatry, 50(5), 410-472. doi:10.1177/0004867416641195

Gao, S., Hendrie, H. C., Hall, K. S., & Hui, S. (1998). The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis. Arch Gen Psychiatry, 55(9), 809-815.

Garcia-Casal, J. A., Loizeau, A., Csipke, E., Franco-Martin, M., Perea-Bartolome, M. V., & Orrell, M. (2017). Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis. Aging & Mental Health, 21(5), 454-467. doi:10.1080/13607863.2015.1132677

Gillette Guyonnet, S., Abellan Van Kan, G., Alix, E., Andrieu, S., Belmin, J., Berrut, G., . . . Vellas, B. (2007). IANA (International Academy on Nutrition and Aging) Expert Group: weight loss and Alzheimer's disease. J Nutr Health Aging, 11(1), 38-48.

Gillette-Guyonnet, S., Andrieu, S., Nourhashemi, F., Gardette, V., Coley, N., Cantet, C., . . . Vellas, B. (2011). Long-term progression of Alzheimer's disease in patients under antidementia drugs. Alzheimers Dement, 7(6), 579-592. doi:10.1016/j.jalz.2011.02.009

Giovagnoli, A. R., Manfredi, V., Parente, A., Schifano, L., Oliveri, S., & Avanzini, G. (2017). Cognitive training in Alzheimer's disease: a controlled randomized study. Neurological Sciences, 38(8), 1485-1493. doi:10.1007/s10072-017-3003-9

Giuli, C., Papa, R., Lattanzio, F., & Postacchini, D. (2016). The Effects of Cognitive Training for Elderly: Results from My Mind Project. Rejuvenation Research, 19(6), 485-494. doi:10.1089/rej.2015.1791

Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from Functional Neuroimaging of a Compensatory Prefrontal Network in Alzheimer's Disease. The Journal of Neuroscience, 23(3), 986-993.

Groot, C., Hooghiemstra, A. M., Raijmakers, P. G., van Berckel, B. N., Scheltens, P., Scherder, E. J., . . . Ossenkoppele, R. (2016). The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. Ageing Res Rev, 25, 13-23. doi:10.1016/j.arr.2015.11.005

Guyatt, G. H., Sackett, D. L., & Cook, D. J. (1993). Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. JAMA, 270(21), 2598-2601.

Hardman, R. J., Kennedy, G., Macpherson, H., Scholey, A. B., & Pipingas, A. (2016). Adherence to a Mediterranean-Style Diet and Effects on Cognition in Adults: A Qualitative Evaluation and Systematic Review of Longitudinal and Prospective Trials. Frontiers in Nutrition, 3, 22. doi:10.3389/fnut.2016.00022

Haskell, W. L., Lee, I. M., Pate, R. R., Powell, K. E., Blair, S. N., Franklin, B. A., . . . Bauman, A. (2007). Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Med Sci Sports Exerc, 39(8), 1423-1434. doi:10.1249/mss.0b013e3180616b27

Heiss, W. D., Kessler, J., Mielke, R., Szelies, B., & Herholz, K. (1994). Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. Dementia, 5(2), 88-98.

Herholz, S. C., & Zatorre, R. J. (2012). Musical Training as a Framework for Brain Plasticity: Behavior, Function, and Structure. Neuron, 76(3), 486-502. doi:https://doi.org/10.1016/j.neuron.2012.10.011

Higgins, J. P. T., Altman, D. G., & Sterne, J. A. C. (2011). Chapter 8: Assessing risk of bias in included studies. In J. P. T. Higgins & S. Green (Eds.), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hill, N. T., Mowszowski, L., Naismith, S. L., Chadwick, V. L., Valenzuela, M., & Lampit, A. (2017). Computerized Cognitive Training in Older Adults With Mild Cognitive Impairment or Dementia: A Systematic Review and Meta-Analysis. Am J Psychiatry, 174(4), 329-340. doi:10.1176/appi.ajp.2016.16030360

Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. British Journal of Psychiatry, 140, 566-572.

Hugo, J., & Ganguli, M. (2014). Dementia and Cognitive Impairment: Epidemiology, Diagnosis, and Treatment. Clinics in geriatric medicine, 30(3), 421-442. doi:10.1016/j.cger.2014.04.001

Huntley, J. D., Gould, R. L., Liu, K., Smith, M., & Howard, R. J. (2015). Do cognitive interventions improve general cognition in dementia? A meta-analysis and meta-regression. BMJ Open, 5, e005247.

Huntley, J. D., Hampshire, A., Bor, D., Owen, A., & Howard, R. J. (2017). Adaptive working memory strategy training in early Alzheimer's disease: randomised controlled trial. The British Journal of Psychiatry, 210(1), 61-66. doi:10.1192/bjp.bp.116.182048

Hänninen, T., Hallikainen, M., Tuomainen, S., Vanhanen, M., & Soininen, H. (2002). Prevalence of mild cognitive impairment: a population-based study in elderly subjects. Acta Neurol Scand, 106(3), 148-154.

Jelcic, N., Agostini, M., Meneghello, F., Bussè, C., Parise, S., Galano, A., . . . Cagnin, A. (2014). Feasibility and efficacy of cognitive telerehabilitation in early Alzheimer's disease: a pilot study. Clin Interv Aging, 9, 1605-1611.

Jelcic, N., Cagnin, A., Meneghello, F., Turolla, A., Ermani, M., & Dam, M. (2012). Effects of lexical-semantic treatment on memory in early Alzheimer disease: an observer-blinded randomized controlled trial. Neurorehabilitation and Neural Repair, 26(8), 949-956.

Jellinger, K. A., & Korczyn, A. D. (2018). Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? BMC Med, 16, 34. doi:10.1186/s12916-018-1016-8

Kaduszkiewicz, H., Zimmermann, T., Beck-Bornholdt, H. P., & van den Bussche, H. (2005). Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. The British Medical Journal, 331(7512), 321-327. doi:10.1136/bmj.331.7512.321

Kandiah, N., Pai, M.-C., Senanarong, V., Looi, I., Ampil, E., Park, K. W., . . . Christopher, S. (2017). Rivastigmine: the advantages of dual inhibition of acetylcholinesterase and butyrylcholinesterase and its role in subcortical vascular dementia and Parkinson's disease dementia. Clinical Interventions in Aging, 12, 697-707. doi:10.2147/CIA.S129145

Kawashima, R., Okita, K., Yamazaki, R., Nobumoto, T., Yoshida, H., Taira, M., . . . Sugimoto, K. (2005). Reading aloud and arithmetic calculation improve frontal function of people with dementia. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 60(3), 380-384.

Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. Syst Rev, 6(1), 259. doi:10.1186/s13643-017-0632-2

Kim, S. (2015). Cognitive rehabilitation for elderly people with early-stage Alzheimer's disease. J Phys Ther Sci, 27, 543-546.

Koltai, D. C., Welsh-Bohmer, K. A., & Schmechel, D. E. (2001). Influence of anosognosia on treatment outcome among dementia patients. Neuropsychol Rehabil, 11(3/4), 455-475.

Kurz, A. F., Leucht, S., & Lautenschlager, N. T. (2011). The clinical significance of cognition focused interventions for cognitively impaired older adults: a systematic review of randomized controlled trials. Int Psychogeriatr, 23(9), 1364-1375.

Kurz, A., Thöne-Otto, A., Cramer, B., Egert, S., Frölich, L., Gertz, H. J., . . . Werheid, K. (2012). CORDIAL: cognitive rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease: a multicenter, randomized, controlled trial. Alzheimer Dis Assoc Disord, 26(3), 246-253.

Laakkonen, M.-L., Kautiainen, H., Hölttä, E., Savikko, N., Tilvis, R. S., Strandberg, T. E., & Pitkälä, K. H. (2016). Effects of Self-Management Groups for People with Dementia and Their Spouses—Randomized Controlled Trial. Journal of the American Geriatrics Society, 64(4), 752-760. doi:10.1111/jgs.14055

Lacey, L. A., Niecko, T., Leibman, C., Liu, E., & Grundman, M. (2013). Association between illness progression measures and total cost in Alzheimer's disease. J Nutr Health Aging, 17(9), 745-750. doi:10.1007/s12603-013-0368-1

Lalanne, J., Gallarda, T., & Piolino, P. (2015). 'The castle of remembrance': New insights from a cognitive training programme for autobiographical memory in Alzheimer's disease. Neuropsychological Rehabilitation, 25(2), 254-282.

Lampit, A., Hallock, H., & Valenzuela, M. (2014). Computerized cognitive training in cognitively healthy older adults: a systematic review and meta-analysis of effect modifiers. PLOS Medicine, 11(11), e1001756. doi:10.1371/journal.pmed.1001756

Langa, K. M., Foster, N. L., & Larson, E. B. (2004). Mixed dementia: Emerging concepts and therapeutic implications. JAMA, 292(23), 2901-2908. doi:10.1001/jama.292.23.2901

Lazarus, L. W., Newton, N., Cohler, B., Lesser, J., & Schweon, C. (1987). Frequency and presentation of depressive symptoms in patients with primary degenerative dementia. Am J Psychiatry, 144(1), 41-45.

Lee, G. Y., Yip, C. C., Yu, E. C., & Man, D. W. (2013). Evaluation of a computer-assisted errorless learning-based memory training program for patients with early Alzheimer's disease in Hong Kong: a pilot study. Clinical Interventions in Aging, 8, 623-633.

Liberati, G., Raffone, A., & Belardinelli, M. O. (2012). Cognitive reserve and its implications for rehabilitation and Alzheimer's disease. Cogn Process, 13, 1-12.

Loewenstein, D. A., Acevedo, A., Czaja, A. J., & Duara, R. (2004). Cognitive rehabilitation of mildly impaired Alzheimer disease patients on cholinesterase inhibitors. American Journal of Geriatric Psychiatry, 12, 395-402.

Lucca, U., Tettamanti, M., Logroscino, G., Tiraboschi, P., Landi, C., Sacco, L., . . . Recchia, A. (2015). Prevalence of dementia in the oldest old: the Monzino 80-plus population based study. Alzheimers Dement, 11(3), 258-270.e253. doi:10.1016/j.jalz.2014.05.1750

Maci, T., Le Pira, F., Quattrocchi, G., Di Nuovo, S., Perciavalle, V., & Zappia, M. (2012). Physical and cognitive stimulation in Alzheimer disease. The GAIA Project: a pilot study. Am J Alzheimers Dis Other Demen, 27(2), 107-113.

Mackenzie, I. R. A., Neumann, M., Bigio, E. H., Cairns, N. J., Alafuzoff, I., Kril, J., . . . Mann, D. M. A. (2010). Nomenclature and nosology for neuropathologic subtypes of frontotemporal lobar degeneration: an update. Acta neuropathologica, 119(1), 1-4. doi:10.1007/s00401-009-0612-2

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. Hippocampus, 16(12), 1091-1101. doi:10.1002/hipo.20233

Mahoney, R., Regan, C., Katona, C., & Livingston, G. (2005). Anxiety and depression in family caregivers of people with Alzheimer disease: the LASER-AD study. Am J Geriatr Psychiatry, 13(9), 795-801. doi:10.1176/appi.ajgp.13.9.795

Martyr, A., & Clare, L. (2012). Executive function and activities of daily living in Alzheimer's disease: a correlational meta-analysis. Dementia and Geriatric Cognitive Disorders, 33(2-3), 189-203. doi:10.1159/000338233

McDermott, O., Charlesworth, G., Hogervorst, E., Stoner, C., Moniz-Cook, E., Spector, A., . . . Orrell, M. (2018). Psychosocial interventions for people with dementia: a synthesis of systematic reviews. Aging Ment Health, 1-11. doi:10.1080/13607863.2017.1423031

McKeith, I. G., Dickson, D. W., Lowe, J., Emre, M., O'Brien, J. T., Feldman, H., . . . Yamada, M. (2005). Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology, 65(12), 1863-1872. doi:10.1212/01.wnl.0000187889.17253.b1

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease. Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology, 34(7), 939-944. doi:10.1212/wnl.34.7.939

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Jr., Kawas, C. H., . . . Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7(3), 263-269. doi:10.1016/j.jalz.2011.03.005

Memory Disorders. Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim, Societas Gerontologica Fennica, the Finnish Neurological Society, the Finnish Psychogeriatric Association, and the Finnish Association for General Practice. Helsinki: The Finnish Medical Society Duodecim, 2017 (referred May 15, 2018). Available online at: www.kaypahoito.fi

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cognitive Psychology, 41(1), 49-100. doi:10.1006/cogp.1999.0734

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med, 6(7), e1000097. doi:10.1371/journal.pmed.1000097

Mohs, R. C., Marin, D., Green, C. R., & Davis, K. L. (1997). The Alzheimer's Disease Assessment Scale: Modifications That Can Enhance its Use in Future Clinical Trials. In R. E. Becker, E. Giacobini, J. M. Barton, & M. Brown (Eds.), Alzheimer Disease: From Molecular Biology to Theraphy (pp. 407-411). Boston, MA: Birkhäuser Boston.

Muurinen, S., Savikko, N., Soini, H., Suominen, M., & Pitkälä, K. (2015). Nutrition and psychological well-being among long-term care residents with dementia. The Journal of Nutrition, Health & Aging, 19(2), 178-182. doi:10.1007/s12603-014-0519-z

Neely, A. S., Vikstrom, S., & Josephsson, S. (2009). Collaborative memory intervention in dementia: caregiver participation matters. Neuropsychol Rehabil, 19(5), 696-715.

Nelson, L., & Tabet, N. (2015). Slowing the progression of Alzheimer's disease; what works? Ageing Research Reviews, 23, 193-209. doi:10.1016/j.arr.2015.07.002

Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., . . . Kivipelto, M. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. The Lancet, 385(9984), 2255-2263. doi:10.1016/S0140-6736(15)60461-5

Niu, Y., Tan, J., Guan, J., Zhang, Z., & Wang, L. (2010). Cognitive stimulation therapy in the treatment of neuropsychiatric symptoms in Alzheimer's disease: a randomized controlled trial. Clinical Rehabilitation, 24, 1102-1111.

O'Brien, J. T., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., . . . DeKosky, S. T. (2003). Vascular cognitive impairment. The Lancet Neurology, 2(2), 89-98. doi:https://doi.org/10.1016/S1474-4422(03)00305-3

O'Brien, J. T., & Thomas, A. (2015). Vascular dementia. The Lancet, 386(10004), 1698-1706. doi:https://doi.org/10.1016/S0140-6736(15)00463-8

Official Statistics of Finland. (2014). Educational structure of population [e-publication]. ISSN=2242-2919. Helsinki: Statistics Finland [referred: 16.9.2018]. Retrieved from http://www.stat.fi/til/vkour/2014/vkour_2014_2015-11-05_tie_001_en.html

Olazarán, J., Muñiz, R., Reisberg, B., Peña-Casanova, J., del Ser, T., Cruz-Jentoft, A. J., . . . Sevilla, C. (2004). Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. Neurology, 63, 2348-2353.

Olazarán, J., Reisberg, B., Clare, L., Cruz, I., Pena-Casanova, J., del Ser, T., . . . Muniz, R. (2010). Nonpharmacological therapies in Alzheimer's disease: A systematic review of efficacy. Dementia and Geriatric Cognitive Disorders, 30, 161-178. doi:doi: 10.1159/000316119

Oltra-Cucarella, J., Perez-Elvira, R., Espert, R., & Sohn McCormick, A. (2016). Are cognitive interventions effective in Alzheimer's disease? A controlled meta-analysis of the effects of bias. Neuropsychology, 30(5), 631-652. doi:10.1037/neu0000283

Ott, A., Breteler, M. M. B., van Harskamp, F., Claus, J. J., van der Cammen, T. J. M., Grobbee, D. E., & Hofman, A. (1995). Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study. BMJ, 310(6985), 970.

Pasquier, F., Richard, F., & Lebert, F. (2004). Natural history of frontotemporal dementia: comparison with Alzheimer's disease. Dement Geriatr Cogn Disord, 17(4), 253-257. doi:10.1159/000077148

Peña-Casanova, J., Sánchez-Benavides, G., de Sola, S., Manero-Borrás, R. M., & Casals-Coll, M. (2012). Neuropsychology of Alzheimer's Disease. Archives of Medical Research, 43(8), 686-693. doi:10.1016/j.arcmed.2012.08.015

Perez, L., Helm, L., Sherzai, A. D., Jaceldo-Siegl, K., & Sherzai, A. (2012). Nutrition and vascular dementia. The Journal of Nutrition, Health & Aging, 16(4), 319-324. doi:10.1007/s12603-012-0042-z

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer's disease. A critical review. Brain, 122, 383-404.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. Arch Neurol, 56(3), 303-308.

Pietilä, P., Poutiainen, E., Nukari, J., Launiainen, H., Arifullen-Hämäläinen, U., Sarajuuri, J., & Koskinen, S. (2017). Kognitiivisesti painottunut monimuotoinen kuntoutus kohentaa muistisairaan mielialaa ja tukee läheisen jaksamista. Psykologia, 52(5), 356-375.

Piras, F., Carbone, E., Faggian, S., Salvalaio, E., Gardini, S., & Borella, E. (2017). Efficacy of cognitive stimulation therapy for older adults with vascular dementia. Dementia & Neuropsychologia, 11(4), 434-441. doi:10.1590/1980-57642016dn11-040014

Pitkälä, K. H., Laurila, J. V., Strandberg, T. E., Kautiainen, H., Sintonen, H., & Tilvis, R. S. (2008). Multicomponent geriatric intervention for elderly inpatients with delirium: effects on costs and health-related quality of life. J Gerontol A Biol Sci Med Sci, 63(1), 56-61.

Pitkälä, K. H., Routasalo, P., Kautiainen, H., & Tilvis, R. S. (2009). Effects of psychosocial group rehabilitation on health, use of health care services, and mortality of older persons suffering from loneliness: a randomized, controlled trial. J Gerontol A Biol Sci Med Sci, 64(7), 792-800. doi:10.1093/gerona/glp011

Pitkälä, K. H., Poysti, M. M., Laakkonen, M. L., Tilvis, R. S., Savikko, N., Kautiainen, H., & Strandberg, T. E. (2013). Effects of the Finnish Alzheimer disease exercise trial (FINALEX): a randomized controlled trial. JAMA Intern Med, 173(10), 894-901. doi:10.1001/jamainternmed.2013.359

Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement, 9(1), 63-75.

Prince, M. J., Wimo, A., Guerchet, M. M., Ali, G. C., Wu, Y.-T., & Prina, M. (2015). World Alzheimer Report 2015 - The Global Impact of Dementia. London: Alzheimer's Disease International.

Qiu, C., von Strauss, E., Bäckman, L., Winblad, B., & Fratiglioni, L. (2013). Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. Neurology, 80, 1888-1894. doi: 10.1212/WNL.1210b1013e318292a31

Quayhagen, M. P., Quayhagen, M., Corbeil, R. R., Hendrix, R. C., Jackson, J. E., Snyder, L., & Bower, D. (2000). Coping with dementia: evaluation of four nonpharmacologic interventions. Int Psychogeriatr, 12(2), 249-265.

Quayhagen, M. P., Quayhagen, M., Corbeil, R. R., Roth, P. A., & Rodgers, J. A. (1995). A dyadic remediation program for care recipients with dementia. Nurs Res, 44(3), 153-159.

Rabipour, S., & Raz, A. (2012). Training the brain: fact and fad in cognitive and behavioral remediation. Brain Cogn, 79(2), 159-179. doi:10.1016/j.bandc.2012.02.006

Rahkonen, T., Eloniemi-Sulkava, U., Rissanen, S., Vatanen, A., Viramo, P., & Sulkava, R. (2003). Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry, 74(6), 720-724.

Ranasinghe, K. G., Rankin, K. P., Lobach, I. V., Kramer, J. H., Sturm, V. E., Bettcher, B. M., . . . Miller, B. L. (2016). Cognition and neuropsychiatry in behavioral variant frontotemporal dementia by disease stage. Neurology, 86(7), 600-610. doi:10.1212/wnl.0000000000002373

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J., . . . Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain, 134(9), 2456-2477. doi:10.1093/brain/awr179

Rebok, G. W., Ball, K., Guey, L. T., Jones, R. N., Kim, H., King, J. W., . . . Willis, S. L. (2014). Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc, 62, 16-24.

Reijnders, J., van Heugten, C., & van Boxtel, M. (2013). Cognitive interventions in healthy older adults and people with mild cognitive impairment: A systematic review. Ageing Research Reviews, 12, 263-275. doi:doi.org/10.1016/j.arr.2012.07.003

Reitan, R. M. (1955). The relation of the Trail Making Test to organic brain damage. Journal of Consulting Psychology, 19, 393-394.

Ritchie, K. (2004). Mild cognitive impairment: an epidemiological perspective. Dialogues in Clinical Neuroscience, 6(4), 401-408.

Robertson, I. H., & Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. Psychol Bull, 125(5), 544-575.

Rockwood, K. (2002). Vascular cognitive impairment and vascular dementia. Journal of the Neurological Sciences, 203-204, 23-27. doi:https://doi.org/10.1016/S0022-510X(02)00255-1

Román, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., . . . Scheinberg, P. (1993). Vascular dementia. Neurology, 43(2), 250.

Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. American Journal of Psychiatry, 141, 1356-1364.

Routasalo, P. E., Tilvis, R. S., Kautiainen, H., & Pitkala, K. H. (2009). Effects of psychosocial group rehabilitation on social functioning, loneliness and well-being of lonely, older people: randomized controlled trial. Journal of Advanced Nursing, 65, 297-305.

Sadowsky, C. H., & Galvin, J. E. (2012). Guidelines for the Management of Cognitive and Behavioral Problems in Dementia. The Journal of the American Board of Family Medicine, 25(3), 350-366. doi:10.3122/jabfm.2012.03.100183

Satizabal, C. L., Beiser, A. S., Chouraki, V., Chêne, G., Dufouil, C., & Seshadri, S. (2016). Incidence of Dementia over Three Decades in the Framingham Heart Study. New England Journal of Medicine, 374(6), 523-532. doi:10.1056/NEJMoa1504327

Scheltens, P., Twisk, J. W., Blesa, R., Scarpini, E., von Arnim, C. A., Bongers, A., . . . Kamphuis, P. J. (2012). Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. J Alzheimers Dis, 31(1), 225-236. doi:10.3233/jad-2012-121189

Schneider, J. A., Arvanitakis, Z., Bang, W., & Bennett, D. A. (2007). Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology, 69(24), 2197.

Schneider, L. S., Dagerman, K. S., & Insel, P. (2005). Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA, 294(15), 1934-1943. doi:10.1001/jama.294.15.1934

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ, 340. doi:10.1136/bmj.c332

Serrano-Pozo, A., Frosch, M. P., Masliah, E., & Hyman, B. T. (2011). Neuropathological Alterations in Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine:, 1(1), a006189. doi:10.1101/cshperspect.a006189

Shah, R. C., Kamphuis, P. J., Leurgans, S., Swinkels, S. H., Sadowsky, C. H., Bongers, A., . . . Bennett, D. A. (2013). The S-Connect study: results from a randomized, controlled trial of Souvenaid in mild-to-moderate Alzheimer's disease. Alzheimer's Research & Therapy, 5(6), 59. doi:10.1186/alzrt224

Sheehan, B. (2012). Assessment scales in dementia. Therapeutic Advances in Neurological Disorders, 5(6), 349-358. doi:10.1177/1756285612455733

Sintonen, H. (2001). The 15D instrument of health-related quality of life: properties and applications. Ann Med, 33, 328-336.

Sitzer, D. I., Twamley, E. W., & Jeste, D. V. (2006). Cognitive training in Alzheimer's disease: A meta-analysis of the literature. Acta Psychiatr Scand, 114, 75-90.

Skelly, J., & Flint, A. J. (1995). Urinary Incontinence Associated with Dementia. Journal of the American Geriatrics Society, 43(3), 286-294. doi:10.1111/j.1532-5415.1995.tb07341.x

Slachevsky, A., Villalpando, J., Sarazin, M., Hahn-Barma, V., Pillon, B., & Dubois, B. (2004). Frontal assessment battery and differential diagnosis of frontotemporal dementia and alzheimer disease. Archives of Neurology, 61(7), 1104-1107. doi:10.1001/archneur.61.7.1104

Smith, G. E., Housen, P., Yaffe, K., Ruff, R., Kennison, R. F., Mahncke, H. W., & Zelinski, E. M. (2009). A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study. Journal of the American Geriatrics Society, 57(4), 594-603. doi:10.1111/j.1532-5415.2008.02167.x

Sotaniemi, M., Pulliainen, V., Hokkanen, L., Pirttilä, T., Hallikainen, I., Soininen, H., & Hänninen, T. (2012). CERAD-neuropsychological battery in screening mild Alzheimer's disease. Acta Neurologica Scandinavica, 125(1), 16-23. doi:10.1111/j.1600-0404.2010.01459.x

Spector, A., Orrell, M., & Hall, L. (2012). Systematic review of neuropsychological outcomes in dementia from cognition-based psychological interventions. Dement Geriatr Cogn Disord, 34, 244-255.

Spector, A., Thorgrimsen, L., Woods, B., Royan, L., Davies, S., Butterworth, M., & Orrell, M. (2003). Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry, 183, 248-254.

Spironelli, C., Bergamaschi, S., Mondini, S., Villani, D., & Angrilli, A. (2013). Functional plasticity in Alzheimer's disease: effect of cognitive training on language-related ERP components. Neuropsychologia, 51(8), 1638-1648. doi:10.1016/j.neuropsychologia.2013.05.007

Stern, R. G., Mohs, R. C., Davidson, M., Schmeidler, J., Silverman, J., Kramer-Ginsberg, E., . . . Davis, K. L. (1994). A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration. Am J Psychiatry, 151(3), 390-396. doi:10.1176/ajp.151.3.390

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol, 11(11), 1006-1012. doi:10.1016/s1474-4422(12)70191-6

Stinton, C., McKeith, I., Taylor, J.-P., Lafortune, L., Mioshi, E., Mak, E., . . . O'Brien, J. T. (2015). Pharmacological Management of Lewy Body Dementia: A Systematic Review and Meta-Analysis. American Journal of Psychiatry, 172(8), 731-742. doi:10.1176/appi.ajp.2015.14121582

Suominen, M. H., Puranen, T. M., Jyvakorpi, S. K., Eloniemi-Sulkava, U., Kautiainen, H., Siljamaki-Ojansuu, U., & Pitkälä, K. H. (2015). Nutritional Guidance Improves Nutrient Intake and Quality of Life, and May Prevent Falls in Aged Persons with Alzheimer Disease Living with a Spouse (NuAD Trial). J Nutr Health Aging, 19(9), 901-907. doi:10.1007/s12603-015-0558-0

Särkämö, T., Tervaniemi, M., Laitinen, S., Numminen, A., Kurki, M., Johnson, J. K., & Rantanen, P. (2014). Cognitive, Emotional, and Social Benefits of Regular Musical Activities in Early Dementia: Randomized Controlled Study. The Gerontologist, 54(4), 634-650. doi:10.1093/geront/gnt100

Tan, C. C., Yu, J. T., Wang, H. F., Tan, M. S., Meng, X. F., Wang, C., . . . Tan, L. (2014). Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis, 41(2), 615-631. doi:10.3233/jad-132690

Tappen, R. M., & Hain, D. (2014). The effct of in-home cognitive training on functional performance of individuals with mild cognitive impairment and early-stage Alzheimer's disease. Res Gerontol Nurs, 7(1), 14-24.

Tarraga, L., Boada, M., Modinos, G., Espinosa, A., Diego, S., Modera, A., . . . Becker, J. T. (2006). A randomised pilot sudy to assess the efficacy of an interactive multimedia tool of cognitive stimulation in Alzheimer's disease. J Neurol Neurosurg Psychiatry, 77, 1116-1121.

Tikkanen, U. (2016). Omaishoidon arki. Tutkimus hoivan sidoksista. [The everyday life and bonds of the spousal care of the elderly]. Doctoral thesis. Helsinki: Unigrafia.

Trebbastoni, A., Imbriano, L., Podda, L., Rendace, L., Sacchetti, M. L., Campanelli, A., . . . de Lena, C. (2018). Cognitive Training in Patients with Alzheimer's Disease: Findings of a 12-month Randomized Controlled Trial. Current Alzheimer Research, 15(5), 452-461. doi:10.2174/1567205014666171113105044

Tremont, G. (2011). Family Caregiving in Dementia. Medicine and health, Rhode Island, 94(2), 36-38.

Unverzagt, F. W., Guey, L. T., Jones, R. N., Marsiske, M., King, J. W., Wadley, V. G., . . . Tennstedt, S. L. (2012). ACTIVE Cognitive Training and Rates of Incident Dementia. Journal of the International Neuropsychological Society, 18(4), 669-677. doi:10.1017/S1355617711001470

van Heugten, C. M., Ponds, R. W., & Kessels, R. P. (2016). Brain training: hype or hope? Neuropsychol Rehabil, 26(5-6), 639-644. doi:10.1080/09602011.2016.1186101

van Paasschen, J., Clare, L., Yuen, K. S., Woods, R. T., Evans, S. J., Parkinson, C. H., . . . Linden, D. E. (2013). Cognitive rehabilitation changes memory-related brain activity in people with Alzheimer disease. Neurorehabil Neural Repair, 27(5), 448-459. doi:10.1177/1545968312471902

Verhagen, A. P., de Vet, H. C., de Bie, R. A., Kessels, A. G., Boers, M., Bouter, L. M., & Knipschild, P. G. (1998). The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J of Clin Epidemiol, 51, 1235-1241.

Voigt-Radloff, S., de Werd, M. M., Leonhart, R., Boelen, D. H., Olde Rikkert, M. G., Fliessbach, K., . . . Hull, M. (2017). Structured relearning of activities of daily living in dementia: the randomized controlled REDALI-DEM trial on errorless learning. Alzheimers Res Ther, 9(1), 22. doi:10.1186/s13195-017-0247-9

Walker, Z., Possin, K. L., Boeve, B. F., & Aarsland, D. (2015). Lewy body dementias. Lancet, 386(10004), 1683-1697. doi:10.1016/s0140-6736(15)00462-6

Wang, J., Yu, J.-T., Wang, H.-F., Meng, X.-F., Wang, C., Tan, C.-C., & Tan, L. (2015). Pharmacological treatment of neuropsychiatric symptoms in Alzheimer's disease: a systematic review and meta-analysis. Journal of Neurology, Neurosurgery & Psychiatry, 86(1), 101-109.

Wechsler, D. (2008). WMS-III käsikirja. [Wehsler Memory Scale – Third Edition]. Helsinki: Psykologien Kustannus Oy.

Wechsler, D. (2012). WAIS-IV käsikirja. [Wehsler Adult Intelligence scale – Fourth Edition]. Helsinki: Psykologien Kustannus Oy.

Weintraub, S., Wicklund, A. H., & Salmon, D. P. (2012). The Neuropsychological Profile of Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine, 2(4). doi:10.1101/cshperspect.a006171

Willis, S. L., Tennstedt, S. L., Marsiske, M., Ball, K., Elias, J., Koepke, K. M., . . . Wright, E. (2006). Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA, 296(23), 2805-2814.

Wilson, R. S., Segawa, E., Boyle, P. A., Anagnos, S. E., Hizel, L. P., & Bennett, D. A. (2012). The natural history of cognitive decline in Alzheimer's disease. Psychol Aging, 27(4), 1008-1017. doi:10.1037/a0029857

Wimo, A., Guerchet, M., Ali, G. C., Wu, Y. T., Prina, A. M., Winblad, B., . . . Prince, M. (2017). The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's & Dementia, 13(1), 1-7. doi:10.1016/j.jalz.2016.07.150

Woods, B., Aguirre, E., Spector, A. E., & Orrell, M. (2012). Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database Syst Rev, 2, CD005562.

Woods, B., Spector, A., Jones, C., Orrell, M., & Davies, S. (2005). Reminiscence therapy for dementia. Cochrane Database Syst Rev(2), Cd001120. doi:10.1002/14651858.CD001120.pub2

World Health Organization. (2016). International statistical classification of diseases and related health problems - 10th revision, Fifth edition; ICD-10. Geneva: World Health Organization.

Wu, Y.-T., Beiser, A. S., Breteler, M. M. B., Fratiglioni, L., Helmer, C., Hendrie, H. C., . . . Brayne, C. (2017). The changing prevalence and incidence of dementia over time — current evidence. Nature Reviews Neurology, 13, 327. doi:10.1038/nrneurol.2017.63

Wykes, T., Huddy, V., Cellard, C., McGurk, S., & Czobor, P. (2011). A Meta-Analysis of Cognitive Remediation for Schizophrenia: Methodology and Effect Sizes. American Journal of Psychiatry, 168(5), 472-485. doi:10.1176/appi.ajp.2010.10060855

Yaffe, K., Fox, P., Newcomer, R., Sands, L., Lindquist, K., Dane, K., & Covinsky, K. E. (2002). Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA, 287(16), 2090-2097.

Zelinski, E.M. (2009). Far transfer in cognitive training of older adults. Restor Neurol Neurosci, 27(5), 455-471. doi: 10.3233/RNN-2009-0495

Zhuang, J. P., Fang, R., Feng, X., Xu, X. H., Liu, L. H., Bai, Q. K., . . . Chen, S. D. (2013). The impact of human-computer interaction-based comprehensive training on the cognitive functions of cognitive impairment elderly individuals in a nursing home. J Alzheimers Dis, 36(2), 245-251.

Öhman, H., Savikko, N., Strandberg, T. E., Kautiainen, H., Raivio, M. M., Laakkonen, M.-L., . . . Pitkälä, K. H. (2016). Effects of Exercise on Cognition: The Finnish Alzheimer Disease Exercise Trial: A Randomized, Controlled Trial. Journal of the American Geriatrics Society, 64(4), 731-738. doi:10.1111/jgs.14059

Appendices

Appendix 1. Questionnaire concerning background information of participants [Osallistujien taustatietolomake]

Appendix 2. Feedback questionnaire for the intervention group [Interventioryhmän palautekysely]

Appendix 1. Questionnaire concerning background information of participants [Osallistujien taustatietolomake]

MUISTIPOTILAAN TAUSTATIEDOT, TERVEYDENTILA, SAIRAUDET, LÄÄKKEET JA PALVELUT

OMAINEN _____ **PVÄ** _____

1. Nimi _____ **SOTU**_____

2. Tutkittavan koulutus? **3. Ikä** _____

1. kansakoulu tai vähemmän
2. ammattikoulu
3. keskikoulu
4. lukio
5. opistoasteen ammattikoulutus
6. korkeakoulu

4. Missä ammatissa tutkittava toimi pääasiallisesti työssäoloaikanaan?

_____

5. Missä tutkittava asuu?

1. Kotona, yksin
2. Kotona, omaisen kanssa (nimi)_____
3. Palvelutalossa

6. Omainen jolta tietoja saadaan, on

1. Tutkittavan puoliso
2. Tutkittavan lapsi
3. Muu, mikä suhde _____

6. Näkeekö tutkittava riittävästi hyvin liikkua? 1. kyllä 2. en

7. Kuuleeko tutkittava tavallista puhetta? 1. kyllä 2. en

8. Käyttääkö kuulokojetta? 1. kyllä 2. en

9. <u>Pyydä omaista lähettämään epikriisi, lääkelista ja kotihoidon yhteystiedot, jotta diagnoosit ja lääkkeet voidaan todentaa</u>

10. Luetelkaa tähän lääkärin tutkittavalle määräämä säännöllinen lääkitys (päiväpaikasta, kotisairaanhoidosta tai omaiselta - VIIMEISIN)

Lääkitys, annostus

1. _____
2. _____
3. _____
4. _____
5. _____
6. _____
7. _____
8. _____
9. _____
10. _____
11. _____
12. _____

Muut _____

_____

11. Milloin tutkittava on ollut viimeksi sairaalahoidossa?

1____ alle kuukausi sitten
2 ____1-12 kuukautta sitten
3 ____yli vuosi sitten

Missä sairaaloissa viimeisen **viiden vuoden** aikana?

_____
_____
_____
_____

12. Onko lääkäri todennut tutkittavalla seuraavia sairauksia

*sokeritaudin? kyllä ☐ ei ☐
*korkean tai kohonneen verenpaineen? kyllä ☐ ei ☐
*sepelvaltimotaudin eli angina pectoriksen? kyllä ☐ ei ☐
*sydänveritulpan eli sydäninfarktin? kyllä ☐ ei ☐
*sydämen vajaatoiminnan? kyllä ☐ ei ☐
*korkean veren kolesterolipitoisuuden? kyllä ☐ ei ☐
*aivohalvauksen tai aivoverenkiertohäiriön? kyllä ☐ ei ☐
*muistihäiriötä? kyllä ☐ ei ☐
*alaraajojen verenkiertohäiriön? kyllä ☐ ei ☐
*maha- tai pohjukaissuolen haavauman? kyllä ☐ ei ☐
*muun kroonisen suolistosairauden? kyllä ☐ ei ☐
jos on, minkä? _____
*keuhkoastman? kyllä ☐ ei ☐
*kroonisen keuhkoputkentulehduksen? kyllä ☐ ei ☐
*keuhkolaajentuman? kyllä ☐ ei ☐

*nivelreuman? kyllä □ ei □
*nivelkulumia kyllä □ ei □
*syövän? kyllä □ ei □
milloin? _____
mikä syöpä?_____
*kilpirauhasen toimintahäiriön? kyllä □ ei □
jos on, minkä? _____
*jonkin muun pitkäaikaisen sairauden? kyllä □ ei □
jos on, minkä? _____
_____
_____
*Onko teille tehty sydänleikkaus tai sepelvaltimoiden pallolaajennushoito?
kyllä □ ei □
jos on, missä? _____

Kysymme vielä muistisairauteen liittyvistä asioista

13. Missä tutkittava oli tutkimuksissa muistioireiden vuoksi?

_____

14. Missä muistisairauden seuranta tapahtuu nykyisin (alleviivaa yksi tai useampia seuraavista)

a) terveysasemalla
b) sairaalan poliklinikalla
c) yksityislääkärin vastaanotolla
d) ei missään

15. Onko tutkittavalla mielestänne toimiva lääkärisuhde?
1. Kyllä, kuka ja missä _____
2. Ei ole

16. Käykö hänen luonaan kotisairaanhoitaja?
1. Kyllä _____ kertaa kuukaudessa
2. Ei

17. Saako hän kotipalvelua?
1. Kyllä _____kertaa kuukaudessa
2. Ei

KIITOS VASTAUKSISTANNE!

Appendix 2. Feedback questionnaire for the intervention group [Interventioryhmän palautekysely]

Hyvä muistiharjoitteluryhmään osallistunut kuntoutuja,

Kysymme seuraavassa mielipiteitänne tästä tutkimuksesta ja saamastanne kuntoutuksesta, jotta voisimme kehittää toimintaamme. Mielipiteenne on meille erittäin tärkeä.

Päivätoimintapaikka jossa olette osallistunut harjoitteluun:

_____

Oliko ohjelma harjoittelukerroilla riittävän monipuolista?	Kyllä	Ei
Oliko ohjelma harjoittelukerroilla riittävän haastavaa?	Kyllä	Ei
Oliko ohjelma harjoittelukerroilla liian vaikeaa?	Kyllä	Ei
Oliko muistiharjoittelu kannaltanne hyödyllistä?	Kyllä	Ei
Paraniko muistinne harjoittelun ansioita?	Kyllä	Ei

Jos kyllä, niin miten hyöty on näkynyt arkielämässä:

_____

_____

_____

Harjoittelun sisältö

7. Mikä harjoittelussa oli erityisen mieluisaa tai hyödyllistä:

_____

_____

8. Mikä harjoittelussa oli mielestänne turhaa tai huonoa:

_____

_____

9. Mitä muuta haluatte kertoa palautteena meille: _____

_____

_____

Suurkiitos vastauksistanne!

Original publications

I Kallio, E.-L., Öhman, H., Kautiainen, H., Hietanen, M., & Pitkälä, K. (2017). Cognitive Training Interventions for Patients with Alzheimer's Disease: A Systematic Review. Journal of Alzheimer's Disease, 56(4), 1349-1372.[1]

II Kallio, E.-L., Öhman, H., Carlson, S., Kautiainen, H., Hietanen, M., & Pitkälä, K. H. (2017). Feasibility and baseline findings of a Finnish cognitive training (FINCOG) intervention in a randomised controlled trial among community-dwelling persons with dementia. European Geriatric Medicine, 8(3), 245-249.[2]

III Kallio, E.-L., Öhman, H., Hietanen, M., Soini, H., Strandberg, T. E., Kautiainen, H., & Pitkälä, K. H. (2018). Effects of Cognitive Training on Cognition and Quality of Life of Older Persons with Dementia. Journal of the American Geriatrics Society, 66(4), 664-670.[3]

IV Kallio E.-L., Hietanen M, Kautiainen H, Pitkälä K. H. Cognitive Training in Older Adults with Mild to Moderate Dementia: Evidence from a Randomized Controlled Trial (submitted).

The publications were reprinted with the permission from the copyright owners.

Original publications are not included in the electronic version of this dissertation.

---

[1]Reprinted from the Journal of Alzheimer's Disease, Copyright (2017), with permission from IOS Press.

[2]This article has been published in European Geriatric Medicine, Copyright Elsevier (2017).

[3]This article has been published in the Journal of the American Geriatrics Society, Copyright John Wiley and Sons (2018).