THE UNIVERSITY OF
SYDNEY

Timecourse of Cognitive and Brain Adaptation to Cognitive Training in At-risk Elderly

Amit Lampit, Mag(FH)

THE UNIVERSITY OF SYDNEY

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Faculty of Medicine
University of Sydney

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To Michael, Harry, Chao, Ellen and Aileen. Your fingerprints are all over this thesis. Hope it will make you proud.

I feel privileged to call Australia home and honoured to serve at the forefront of the national fight against dementia.

Per aspera ad astra.

Abstract

Maintaining cognitive ability in the elderly is a global priority. In this regard, Computerised cognitive training (CCT) is among the few effective interventions but several gaps in the evidence base limit clinical implementation. Specifically, we do not understand which specific cognitive skills can be effectively targeted, which design features moderate efficacy, or the nature of the underlying neuroplastic mechanisms. To address this problem, three inter-related studies were conducted.

Chapter 2 is the first systematic review to utilise meta-analysis and meta-regression techniques to evaluate randomised controlled trials (RCTs) of tightly-defined CCT in healthy elderly. Three hundred forty-four effect sizes were generated from 37 RCTs, encompassing a total of 4,310 participants. Overall, CCT was effective on memory, working memory, processing speed, attention, language and visuospatial skills, but not on executive function. Type of training program, mode of delivery, session length and training frequency were found to moderate CCT efficacy.

These design features were implemented in the Timecourse Trial (**Chapter 3**), a randomized, double-blind, active controlled longitudinal RCT of CCT in 80 healthy elderly. Significant effects were found on global cognition, memory and processing speed, as well as distinct dose-response curves across domains. These domain-specific gains also followed different decay curves after training cessation, yet positive residual effects were still noted at 12 months follow-up.

Gains in global cognition were next (**Chapter 4**) revealed to be related to discrete functional and structural brain changes using multimodal MRI on a subsample from the Timecourse Trial. Modification of resting-state functional connectivity was found to predict subsequent cognitive gains, gains that were also correlated to structural cortical plasticity.

Overall, these results suggest that CCT is an effective intervention for supporting cognition in the elderly. The field may do well to now focus on improving standards, large-scale trials and a further understanding of biological mechanisms.

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Chapter 1: Introduction

But, it is said, memory dwindles. No doubt, unless you keep it in practice, or if you happen to be somewhat dull by nature.

Marcus Tullius Cicero, 44 BCE

Human ageing has been traditionally associated with an inevitable course of cognitive decline, but it is now clear that regeneration and experience-dependent plasticity is possible in the ageing brain when appropriate interventions are applied[1]. With advanced age the brain is at greater risk of a range of degenerative processes that can result in cognitive impairment and dementia, a severe and terminal loss of cognition and independence[2]. At a global scale, declining fertility rates and enhanced longevity have brought about pervasive, enduring, and largely irreversible changes to the age-structure of national populations[3]. These sociodemographic transformations underpin a growing recognition that age-related cognitive decline is one of the key challenges of the century[4].

Whilst the neurobiological mechanisms of age-related cognitive decline and dementia are not fully understood[2], it is clear that individual exposure and experience across the lifespan are instrumental in defining age-related cognitive morbidity[5,6]. Indeed, a growing body of epidemiological studies show a clear link between several lifestyle factors and dementia risk, suggesting that some lifestyle modifications may be protective against cognitive decline[7]. However, the overall evidence base for primary dementia prevention of interventional lifestyle modifications is currently limited[8].

This chapter will therefore introduce the potential role of **computer-assisted cognitive training** (CCT) as a means to improve cognition and reduce the risk of

cognitive decline in healthy ageing. It begins with a brief overview of healthy ageing, mild cognitive impairment (MCI) and dementia, three key stages in the cognitive spectrum of late life. It then discusses dementia prevention strategies, with a focus on the relationship between cognitive activity and dementia risk. Finally, it provides a general introduction to CCT, its development and the current state of the literature on CCT in older adults.

1.1 Ageing, Cognition and Age-related Cognitive Decline

The proportion of people around the world over 65 years of age has grown from 8% in 1950 to 11% today but is expected to double by mid-century[3]. The growth curve is expected to decelerate in the second half of the century, reaching about one-third of global population in 2100[9]. The one-third mark is expected to occur before 2050 in several regions, including Europe, Japan and Oceania, where current fertility and mortality rates have already caused significant demographic changes[9]. Approximately 3.2 million Australians are aged over 65 (14% of total population), and the age brackets 65-74 and >85 are the fastest growing segments in Australia[10]. China may face even greater demographic challenges, as growth in the >65 age bracket is coinciding with significant shrinkage in the working-age population[11]. The clear link between advanced age and morbidity implies that the challenges on the healthcare system are, immediate, acute and escalating[5].

Increasing longevity is not only a global challenge but also an opportunity for testing the impact of cognition-enhancing interventions to prevent or delay **age-related cognitive decline** (ARCD). As evidence of cohort effects in physical and cognitive morbidity accumulate[5,12,13], and the interest in delaying retirement age and redistributing work across the age brackets is growing[14,15], there is increased

likelihood that cognition-enhancing interventions could produce substantial societal impact.

1.1.1 Normal Cognitive Ageing

Whilst prescriptive definitions of 'normal' or 'healthy' cognitive ageing remain elusive, most older adults are psychometrically within the normal range of the cognitive ageing continuum depicted in **Figure 1.1**[16,17]. Here, the general premise of normal ageing is an absence of a diagnosed cognitive impairment[18], i.e., exclusion of performance on one or more neuropsychological tests below the 10th percentile. As almost all older adults tend to show some degree of deterioration in cognitive performance compared to younger adults[2,19], it follows that so-called normal cognitive ageing allows for a degree of cognitive decline up to a normative level defined by respective age-, sex- and education-matched data[18]. Cognitive performance below one-to-two standard deviations (SD) of the norm generally marks the difference between normal cognitive ageing and **mild cognitive impairment** (MCI) (further defined below) [20].

While convenient for both clinical and research purposes, the premise of normal ageing raises several important issues. First, it implies acceptance of ARCD as a natural part of ageing. In an ageing world, tacit acceptance of this notion and failure to take measures to combat this phenomena may turn out to be extremely expensive[15]. This is mainly due to the growing importance of older adults in the labour market, while jobs are becoming more cognitively demanding in today's knowledge economy[14,21]. Hence, initiatives that effectively maintain and enhance cognitive performance in late life would not only decrease dependency ratios, but are arguably a prerequisite for economic stability.

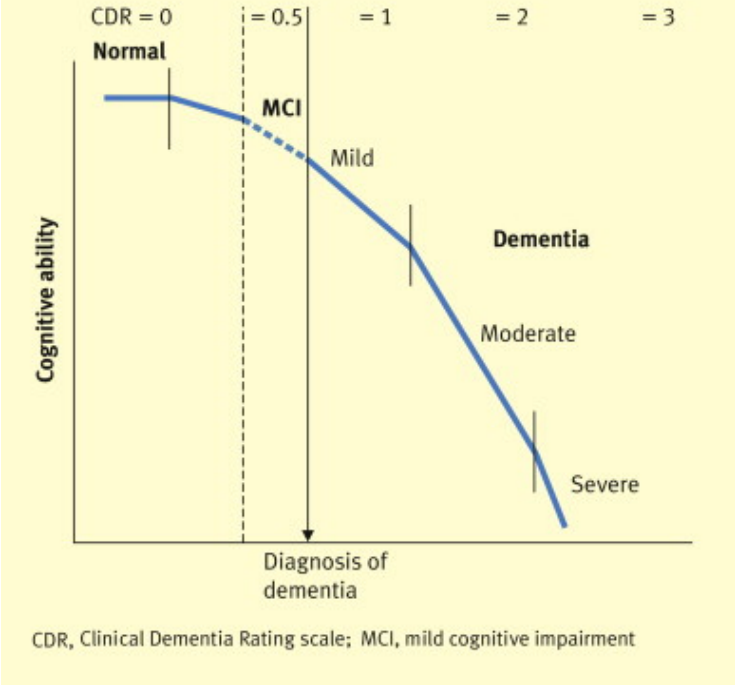


Figure 1.1: The spectrum of cognitive impairment
Source: reproduced from Bullock[22]

Second, normal ageing encompasses an extremely heterogeneous set of cognitive profiles (phenotypes) and trajectories[23] that often overlap with those of MCI[24]. Apart from neurodegenerative pathology, cognitive deficiencies may arise for several reasons including, among others, depression[7], low midlife premorbid intelligence[18], sensory impairment[25], sleep disturbance[26], cerebrovascular disease[27], and cardiovascular disease and other physical comorbidities[18]. Thus, individual risk factors and domain-specific impairments, even when still at a preclinical stage, should be addressed in order to prevent subsequent decline.

Finally, up to 30% of older adults with normal cognitive performance may have clinically silent Alzheimer's disease (AD) pathology such as amyloid-β plaques, which may or may not develop into clinical dementia in later life[28,29]. Therefore, psychometrically normal cognition at a singe timepoint does not rule out the need for periodical evaluation, as every additional year of life increases the risk of dementia. In this way, the entire normal ageing population can be considered at general risk for

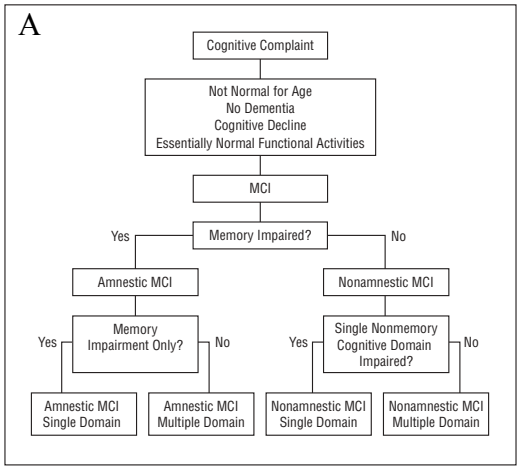
dementia, risk that might be mitigated or exacerbated by the presence of absence other risk factors. For these reasons, there is a strong case for cognitive interventions in the 'normal' cognitively ageing population for the purpose of primary prevention of cognitive decline and dementia.

1.1.2 Mild Cognitive Impairment

MCI involves cognitive decline greater than expected for an individual's age and education level but that does not interfere notably with activities of daily life, and is a frequent precursor of overt dementia[30]. The prevalence rate of MCI is estimated at 10-20% of the elderly (>65) population[31], but prevalence and incidence figures vary significantly, mostly due competing operational definitions and incorrect diagnoses[32,33]. Pusswald et al[24], for example, compared two methods for MCI diagnosis in a cohort of memory clinic outpatients. In their study, 84.3% of the cohort was diagnosed as MCI using one method, but prevalence in the same cohort using a different method was less then half (39.5%).

MCI is a broad term for a range of cognitive deficits, and several definitions have been proposed to differentiate it from normal ageing and to improve its diagnostic and prognostic value. The most notable differentiation is between **amnestic and nonamnestic MCI** (aMCI and naMCI, respectively) as well as **single- and multidomain** MCI [31]. The difference between aMCI and naMCI is the presence of memory impairments, and multidomain MCI denotes that more than one domain (in addition to memory in aMCI) is impaired. The neuropsychological differentiation can be further categorised by the probable aetiology of the impairment, including, among others, AD, vascular dementia (VaD), frontotemporal dementia (FTD), psychiatric

disorders and medical conditions such as metabolic deficiencies and head trauma, or a combination of several sources[34] (see **Figure 1.2**).



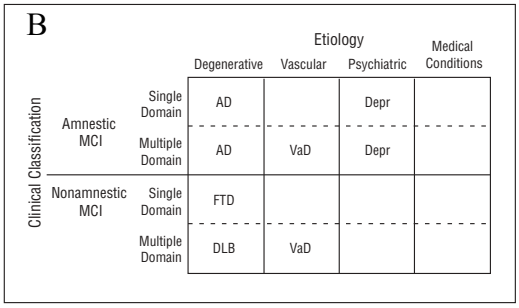


Figure 1.2: MCI types and aetiology
a) diagnostic flowchart for aMCI/naMCI; b) possible MCI aetiologies.
Source: Adapted from Petersen & Morris[34]

In a recent position statement, Albert et al[20] set out four diagnostic characteristics for MCI: concern regarding change in the patient's cognition, impairment (>1 standard deviation from the matched age and education norm) in one or more cognitive domains, preservation of independence in functional abilities, and no dementia, albeit with evidence of cognitive deterioration. The statement recommends incorporating AD biomarkers in the diagnostic process to assess whether the observed MCI symptoms are likely to be early signs of AD, as MCI patients, particularly aMCI, are about 10 times more likely to develop dementia than those with normal cognition at the same age strata and thus may benefit from secondary prevention interventions[31,33,35]. Conversely, most MCI will remain stable or revert to normal cognition[31,32], and since the benefits of pharmacological interventions in MCI are limited[35], the clinical logic of pharmacological interventions to prevent conversion from MCI to dementia is unclear.

MCI represent some degree of deviation from normal cognition and is an important dementia risk factor[31,33], but is it a diagnostic entity in its own right or simply

unnecessary labelling of the effect of age on cognition[36]? Differential diagnosis between MCI, normal cognition and dementia is imprecise[20,34], and prognosis is hard to predict. Rather than being described as a medical syndrome requiring specific interventions, MCI might be better thought of as a warning sign for possible cognitive deterioration and clear reason for frequent evaluation and lifestyle change. That said, it is clear that the field in general is gravitating towards the (still controversial) medicalization of MCI-like syndromes, as evident by the inclusion of Mild Neurocognitive Disorder in DSM-V[37].

1.1.3 Dementia

Dementia is an umbrella term that refers to various cognitive, functional and behavioural syndromes related to neurodegeneration[33]. The 10th revision of the International Statistical Classification of Diseases (ICD-10) defines dementia as disturbance in higher cortical functions, which are accompanied with deterioration in emotional control, social behaviour, or motivation, but without loss of consciousness[38]. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) replaces dementia with the term Major Neurocognitive Disorder to emphasise the existence of such deficits beyond the realm of ageing as in the case of Human immunodeficiency virus (HIV) and brain injury.[37] For the sake of consistency, this thesis will use the term dementia despite the changes in nomenclature.

The diagnostic core of dementia is clinical and symptomatic rather than pathological[39]. A recent position statement[40] defines five criteria of symptoms required to diagnose dementia: interference with everyday functioning; decline from earlier level of functioning; exclusion of delirium or major psychiatric disorder;

evidence of impairment from both subjective (informant interview) and objective (neuropsychological or 'bedside' mental status testing) sources; and impairment in two or more of the following domains: memory, reasoning, visuospatial abilities, language functions and behaviour.

Popular cut-off points for operationalising cognitive criteria include the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) score ≥ 18[41], a neuropsychological test that covers multiple cognitive domains often used in clinical trials, or the Mini-mental State Examination[42] <23, a brief screening instrument of global cognition. The severity of the impairment and its effect on global functioning can be assessed using Clinical Dementia Rating (CDR) scale between 1-3[43] (see also **Figure 1.1**).

The most common single aetiology of dementia is AD (accounts to 60-80% of incidence), followed by cerebrovascular disease, dementia with Lewy bodies, FTD, late-stage Parkinson's disease, mixed dementia, Creutzfeldt-Jakob disease, and normal pressure hydrocephalus (for characterisation of the various types see e.g., Thies et al[33]). Importantly, population-based neuropathology studies suggest that multiple pathology is in fact more common than any single pathology, with AD and cerebrovascular disease being the most common combination[44].

Since dementia mainly occurs in late life, global population ageing is associated with a sharp rise of prevalence. A recent systematic review estimated the global prevalence of dementia at 35.6 million people in 2010, and expected that continuation of the status quo would see this number doubles by 2030[45]. However, recent evidence of positive cohort effects in dementia incidence in four Western countries[12,13,46,47], possibly induced by improvements in health and education in these countries, may

suggest that incidence may decelerate in some parts of the developed world. However, 58% of all people with dementia live in low- or middle-income countries, many of them are lagging behind the Western nations in dementia-relevant aspects of public health and education, and the proportion of dementia cases in these countries is expected to rise in accordance with increased lifespan to 63% in 2030 and 70%[4,45] of global prevalence in 2050 (see Figure 1.3**A**). The global cost of dementia was estimated at US$604 billion in 2010, about 1% of the world GDP[48], and is expected to increase faster than prevalence due to rising costs of patient care[49]. Therefore, the world's weakest economies are taking most of the burden of the disease, leading to profound economic and humanitarian pressures. As current pharmacological interventions for dementia provide merely short-term symptomatic relief in a subset of patients[50], preventative strategies that focus on key risk factors are extremely compelling areas for global action[4].

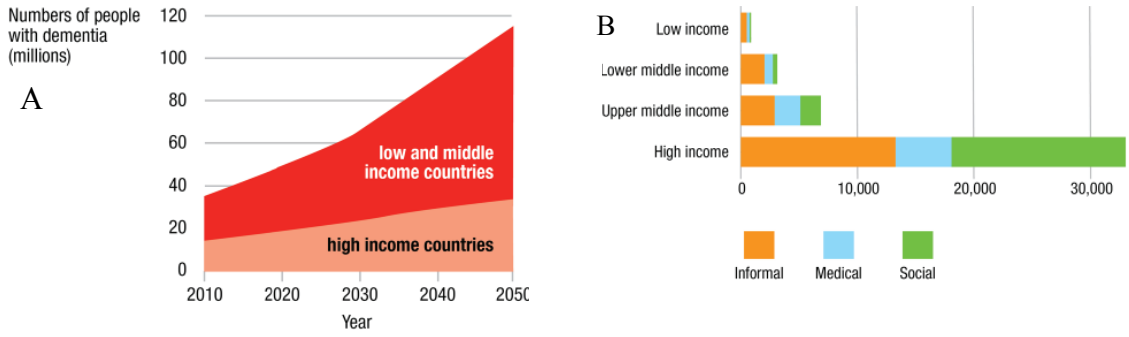


Figure 1.3: Dementia prevalence (A) and costs per patient (B) in high low-to middle-income countries
Source: Wortmann[51]

1.2 Preventing Dementia

Given that AD is the most common cause of dementia and that most cases occur after 65 years[33,45], this review focuses on preventing AD dementia in the elderly population. Furthermore, the main focus here is on modifiable risk factors that can be potentially addressed with interventions, with an emphasis on cognitive inactivity as a

leading modifiable risk factor[7]. However, given that different types of dementia have overlapping risk factors (e.g., cardiovascular disease) and that some interventions may be used for both prevention and moderation of AD, the discussion on cognitive interventions in the second half of this section may also be relevant to other aspects of the dementia epidemic.

1.2.1 The Rationale Behind Prevention

Dementia is associated with three types of costs whose composition vary between different economies (see **Figure 1.3)**[48,51]. Direct medical expenditure (i.e., spending within the health care sector) accounts for about 15% of the total global expenditure on dementia and is the least common expenditure, although dementia contributes to some extent hospitalisation due to other causes[52]. Direct expenditure on social care (institutionalisation) accounts for about a third of total global costs, but vary between 45% of the cost of care in high-income countries to about 13% in low- to middle-income countries. Finally, the cost of informal care (i.e., indirect costs incurred by caring for people with dementia at home or in the community) accounts for 40% in high-income countries and may reach 65% of the economic burden of the disease in lower-middle income countries. These costs may be an underestimation, as the costs may cover multiple parameters, from loss of income to mental health morbidity on behalf of carers.

While much can be made to improve the quality and efficiency of dementia care and medical treatments, there is little argument that reduction of dementia prevalence is a key element in reducing the burden of dementia. The progressive nature of the disease and its late age of onset allow for four types of prevention strategies along the

dementia continuum (Figure 1.1): primary prevention, secondary prevention, tertiary prevention and delayed onset.

Primary prevention aims to reduce the incidence of conversion from normal cognitive function to clinical cognitive impairments (i.e., MCI and dementia)[53]. Secondary prevention targets populations with MCI with or without biomarker evidence of AD pathology in order to prevent further deterioration towards dementia[8]. Tertiary prevention aims to prevent progression in severity of diagnosed dementia, or reduce the degree of functional impairment[50,53]. Finally, delay onset strategies aim to compress the duration of the disease, i.e., to reduce the time between diagnosis and death. Since delayed onset strategies aim to extend the age of diagnosis, they could be thought of as a form of primary prevention.

Several theoretical models have suggested that effective interventions can serve multiple prevention strategies, i.e., delay both onset and progression, bringing about a significant long-term reduction in prevalence[54,55]. For example, a recent Australian model[55] associated every year of delayed onset by an intervention introduced in 2020 with a 7% reduction in prevalence three decades later. The net effect of such interventions on future prevalence depend on a number of factors, including the period of delayed onset and/or progression, the year in which the intervention will be introduced, types of dementia likely to be affected, the timeframe of the model and epidemiological predictions in the relevant geographical region[54,55].

An alternative approach models the effectiveness of specific preventative interventions according to the relative weight of the risk factors reduced by each intervention[7]. Importantly, all of these models rely on assumptions about age-linked increases in prevalence and incidence, which, as mentioned previously, are coming

under increasing scrutiny given evidence for protective cohort effects[12,13,46,47]. Clearly, further epidemiological research is required to test the predictive accuracy of these models.

1.2.2 Preventing Dementia by Targeting Risk Factors

Whilst the theoretical benefit of preventative intervention is clear, establishing empirical evidence has proven exceptionally challenging. Several factors may be responsible, including the heterogeneity of dementia pathogenesis and failure to intervene well ahead of the development of AD pathology[8,17]. More importantly, since incident dementia event rates are low (e.g., 1,8% [95% CI 0.9–3.6] in the age bracket 65-69[13]), previous prevention trials have been underpowered, poorly targeted, or both.

In contrast to the absence of such empirical data, a rapidly growing body of epidemiological studies have identified a range of factors that increase the risk of ageing-related cognitive decline, MCI and conversion to dementia, that may therefore serve as a basis for developing preventative interventions[56].

Two leading risk factors are unmodifiable. First and foremost is increasing age; the incidence of dementia doubles every 5.9 years of age, from 3.1 per 1000 person years in the age bracket 60-64 to 175 at those aged over 95[4]. The second is hereditary, which includes a combination of some genetic variants such as the ε4 form of apolipoprotein E (APOE) gene, other genes that increase dementia-related morbidity (e.g., cardiovascular disease) and early life environmental risk factors[33]. The hereditary nature of mid- and late-life intelligence[17] may play an additional role, as intelligence level is assumed to be inversely related to dementia risk[7].

Conversely, several cardiovascular risk factors have been strongly associated with dementia incidence and seem to be more malleable. These mainly include midlife hypertension, obesity, high cholesterol and diabetes mellitus, as well as high-cholesterol diet, smoking and physical inactivity[7,33,57]. Several interventions inspired from cardiovascular disease prevention trials have been found to be beneficial to maintain cognitive function in the aged. For example, antihypertensive pharmacotherapy in the SYST-EUR Trial (first line calcium channel antagonists) is the only intervention found to reduce dementia incidence in a multicentre randomised controlled trial (RCT)[44], however this has yet to be fully replicated[44]. Cognitive benefits (albeit without evidence of dementia incidence reduction) have also been found in several trials involving smoking cessation[58] and aerobic exercise[59]. However, with the sole exception of SYST-EUR, the association between cardioprotective lifestyle factors (including diet and exercise) and reduced dementia risk are restricted to epidemiological studies and are yet to be translated into effective dementia prevention interventions [16,60].

1.2.3 Mental Activity, Cognitive Lifestyle and Dementia Risk

Epidemiological studies repeatedly link a low level of educational attainment with an increased probability of dementia incidence[7,49,57,61,62], and some studies have further found greater education level associated with compression of cognitive morbidity, possibly due to delayed onset[63] and shortened lifespan following diagnosis[63,64]. Reduced incidence was also associated with a history of engagement in other mentally challenging activities such as occupational complexity[65], cognitively-loaded leisure activities[62] and social engagement[66]. Engagement in an active cognitive lifestyle may stimulate several neurobiological effects, including reduction in cerebral

microvascular disease, increased neuronal density and cortical thickness in the prefrontal cortex[67], as well as increased grey matter volume and lower rate of hippocampal atrophy in late life[68]. While the mechanistic underpinnings of these effects remain unclear, several theoretical explanations have been suggested.

First, there are likely causal relationships between early-life intelligence, educational attainment and occupational complexity[15,17,19], which tend to increase income, engagement in mentally challenging leisure activities and tendency towards healthier behaviour[69]. Similarly, cognitive abilities predict job performance, coping with challenges and thus income[15,70], which, in turn, is associated with decreased dementia risk[49,71] (see **Figure 1.4**). However, some research suggests that different forms of cognitive lifestyle may have distinct effects. For example, dose-dependent and education-independent effects of cognitive activity in late life have been found on the onset of memory decline[72], as well as domain-specific effects of particular cognitive activities[73], which together suggest that activities may differ in the scope and scale of their long term benefits to cognitive function.

Second, complex mental activities across the lifespan (but also premorbid intelligence) are often associated with the concept of *reserve*, which aims to explain "differences between individuals in susceptibility to age-related brain changes and pathology"[74](Stern, p. 1006). Very briefly, one form of the reserve theory proposes that the effect of any neural injury (e.g., AD pathology) on brain and cognitive function is moderated by some premorbid neurophysiological or cognitive capacities (brain and cognitive reserve, respectively). As a result, individuals with higher reserve will require more pathology to induce loss of function compared to individuals with lower reserve, thereby delaying the onset of clinical symptoms and increasing the rate

of decline once the latter has started[75]. Furthermore, cognitive reserve underpins individual differences in strategy and brain function during task performance, which can compensate for pathology and cognitive decline and protect everyday functions[75]. Cognitive reserve has been associated with higher IQ, education, occupational attainment, some leisure activities and social engagement in both epidemiological[61] and imaging studies[75]. The clearest evidence for a compensatory effect of education on dementia is provided by the ECLIPSE multicentre neuropathology collaboration[76], which found that dementia risk for a given level of AD pathology was independently mediated by education level.

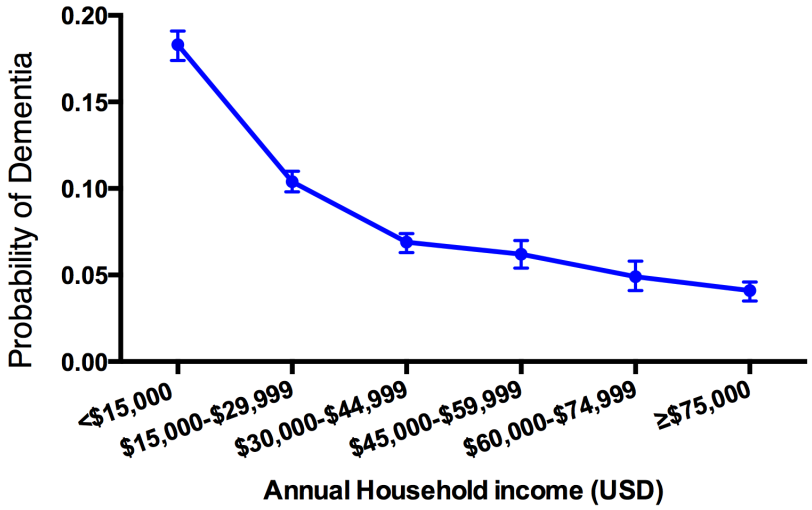


Figure 1.4: Probability of dementia by household income
Source: based on data from Hurd et al[49]. Error bars represent 95% CI

The current definitions of cognitive lifestyle are too broad to provide clear causal links between specific lifestyle modifications and positive cognitive results. More specific evidence, particularly in regard to the type, intensity and implementation of effective cognitive activities is needed to facilitate clinical translation. Nevertheless, interventions that can effectively increase educational attainment and other forms of cognitive stimulation earlier in life may affect cognitive morbidity, especially in the

developing world[77]. In parallel, there is a pressing need to develop specific and effective forms of cognitive enhancement for populations at risk for dementia. This thesis explores the CCT as a possible strategy to meet this challenge.

1.3 CCT in Older Adults: A Primer

The first evidence of cognitive training (CT) go back to Greek poet Simonides of Ceos, who introduced mnemonic *strategy* training in the 5th century BCE "as a technique by which the orator could improve his memory, which would enable him to deliver long speeches from memory with unfailing accuracy[78]" (p. 2). Simonides' *ars memorativa* ("method of places and images") was practiced in rhetoric and monastic contexts through the Middle Ages, along with training aids such as Ramon Lull's combinatory wheels, which helped practitioners to remember Christian concepts through the use of enumeration and grouping. From the late Renaissance onwards, memory training was conceived as a systematic method involving repeated practice on structured tasks, and as an aid for scholastic thinking and logic (rather than merely memorising) as part of the emergence of the scientific method [78,79].

The basic approach of modern-day CT is founded on early trials of cognition-focused psychotherapy in patients with psychiatric illness, brain injuries and other cognitive disorders during the 1960s[80,81]. The notion that the malleability of cognitive performance extends to non-clinical populations became evidently clear in the 1970s, and training programs aimed at improving cognitive performance in the elderly were introduced immediately thereafter[82-84].

Several CT methods have been proposed to target cognition in older adults, based mostly on domain-specific strategy training and multi-modal approaches, which combine strategy training in several neuropsychological domains accompanied with general cognitive stimulation programs (for an overview of the evolution of these interventions, see a review by Lustig et al[85]). Recent years have seen a surge of interest in interventions that involve extended practice on cognitive processes[86-88], including computer-based exercises, which were introduced in the early 1980s and are gaining popularity[89]. By mid-2013, more than 2,000 peer-reviewed articles have been published on the topic (see **Chapter 2**), and the scientific interest in CT applications seems to be growing exponentially (see **1.5**).

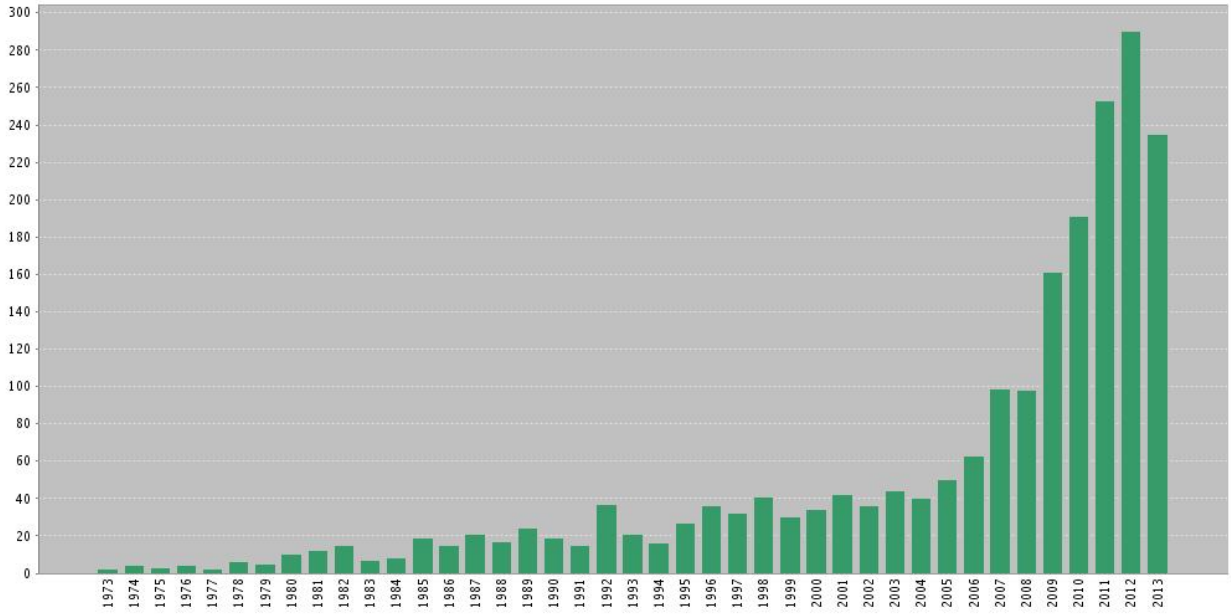


Figure 1.4: Number of publications per year on CT, 1973-August 2013
Source: ISI Web of Knowledge (see **Chapter 2** for search details)

CT is often framed as a type of cognitive remediation[90], defined as "a behavioral training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization[91]" (p. 472), along with other cognitive-based

interventions such as cognitive stimulation and cognitive rehabilitation (see **Figure 1.6**).

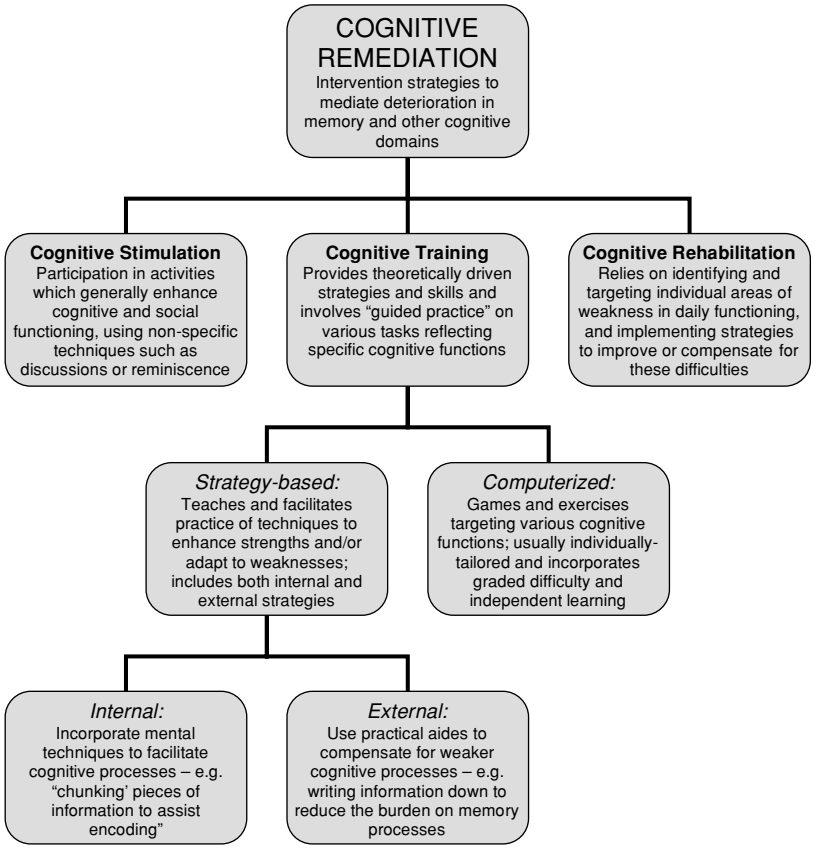


Figure 1.5: A typical view of CT in broader context of remediation
Source: Mowszowski et al[90]

However, it can be argued that classifying CT in the context of cognitive remediation present three problems. First, it incorrectly equates CT with incomparable interventions and obscures the specific methods and effects of CT, as evident by Cochrane reviews that attempt to synthesise a considerably heterogeneous array of non-CT trials (involving e.g., behavioural interventions and general stimulation activities) [92,93]. Second, defining CT this way may incorrectly narrow down the utility of the intervention to clinical populations, whereas training-induced benefits have been documented in high-functioning populations as well. Third, CT is not a generic

intervention, but a rather diverse field with distinct methodologies that are substantially independent from other forms of cognition-focused psychotherapy.

1.3.1 Refining the Nature of Cognitive Training

CT can be defined as repeated practice on one or more tasks with inherent cognitive challenge ('cognitive exercises'), for the purpose of improving performance in specific cognitive domains[50,94,95]. Such improvements are attributed to the process overlap between the exercises and the cognitive domains they target, which can be measured using cognitive tests and/or functional outcomes (transfer tasks). CT can be based on teaching cognitive strategies or on extended practice over hundreds or thousands of trials on tasks that are based on the same theoretical grounds as cognitive tests[86]. Measuring the transferability of the latter kind might be challenging, as some exercises may closely resemble the transfer tasks (for a comprehensive review of transfer of training in older adults, see Zelinski[86]).

Each cognitive exercise usually targets one or two specific cognitive domains, but it is possible to target the same domain using different exercises. That is, just like the pectoralis major muscle can be trained with various resistance exercises (e.g., push ups and bench pressing), response inhibition can be trained using diverse stimuli (e.g., shapes or letters), delivery methods (e.g., computerised or paper-based), speed, levels of stimuli complexity and so on. This does not mean that all response inhibition exercises are born equal – there is indeed a good reason to assume that some would be more efficient, acceptable or effective than others – but the principle that different exercises can target similar cognitive processes still holds, and optimising the content, delivery and dose of CT exercises for specific populations is a growing area of research[96].

In contrast to the nature of CT as a means to deliver practice of cognitive processes, other forms of cognitive remediation use different intervention techniques, such as skill learning, social interactions, engagement in cognitively stimulating activities, coping strategies and individually-tailored CT-like programmes[50,90,94,97]. CT can be combined with remediation techniques, physical exercise and/or pharmacological interventions, but the CT component of such combined approaches is still distinct from the other. Thus, models such as the one depicted in **Figure 1.6** are arguably incorrect, and better description of the interventions in trials of non-pharmacological interventions[98] may help the field to better interpret the evidence.

Moreover, the field lacks coherent terminology to distinguish CT from non-CT interventions, as well as one CT approach from another. Terms such as 'cognitive training[99]', 'brain training[100]', 'brain plasticity-based training[101]', 'mental activity[102]', 'video game training[103]', 'brain exercise[104]', 'cognitive exercise[105]', 'cognitive rehabilitation training[106]' are just a few examples of terms used to describe multi-domain CCT programs in publications. Conversely, using the same term to describe inherently different CT programs may be just as problematic, as such practices establish the idea that all CT programs are identical.

This is not a semantic issue but rather a fundamental problem in the current literature, which slowed down progress[95]. Sloppy terminology could lead to poorly designed trials and unsupported claims, underestimating or overestimating the efficacy of CT[107]. Consequently, systematic reviewers try to pool fundamentally different interventions (both CT and non-CT) into the same meta-analysis, inevitably finding heterogeneous results that are necessarily biased against an indication of efficacy[92,93,108]. It seems therefore that a more detailed taxonomy of cognition-focused

interventions is needed to allow the field to settle questions of efficacy ('does it work?') and then move onto investigation of what works, how it works and for whom[109]. Arguably, it is the latter which are critical for the translation of decades of research into clinical practice.

Rigorously defined CT does not of course rule out the added value of combinatorial multimodal interventions. In fact, results from two recent trials suggest that combining CT with methods from cognitive rehabilitation and stimulation techniques might be effective in older adults. Cheng et al[110] found significant and durable improvements in healthy older adults' global cognition after 24 1-hour group sessions, which combined repeated practice with group discussions, psychoeducation and homework assignments. Similarly, Buschert et al[111] combined group-delivered extended CT practice with cognitive stimulation techniques in patients with MCI, and have shown not only an improvement in global cognition, but also a delay in conversion from MCI to AD compared to a wait-list control group[112]. Unsurprisingly, a meta-analysis of memory training (mnemonics strategies) found group sessions significantly more effective than individual strategy training, citing "social comparison and a resulting feeling of self-efficacy, reactivation, mutual support and reinforcement among the trainees, or enhanced motivation" (p. 250) as key possible explanation for the mediating effect[113]. While the mechanisms underlying the added value of such 'non-specific' effects to CT efficacy are unclear, there may be a case for complementing CT exercises with other forms of stimulation, similar to cognitive rehabilitation methods in schizophrenia[97].

1.3.2 Computer-based CT (CCT)

The following section aims to lay the technical groundwork for the meta-analysis of CCT discussed in **Chapter 2 and the** RCT described in **Chapter 3.**

CCT has several advantages over traditional paper-and-pencil CT, including the possibility to create engaging, game-like exercises, accurate and rapid individual feedback and adaptivity, low administration costs and the option to combine auditory with visual stimuli[95,114,115]. CCT-based interventions can be distinguished by three design features, namely, platform, content and method of delivery. Defining these features is important because as discussed earlier inconsistent terminology hampers understanding and implementation of research results.

1.3.3 Technical Platforms

Most CCT trials to date have used personal computers (PCs), with the CCT software installed on the PC hard drive, using mice and keyboards. Other input devices include touchscreens, joysticks, and – especially in early trials – button boxes. The advent of the internet brought about a surge in online CCT, whereby the user does not posses a copy of the CCT program, and the provider has absolute control over the provision, content and data generated by the software. This feature allows greater flexibility and frequent updates of the software, interfaces with other platforms (e.g., emails and social media), creating performance norms, monitoring compliance and data analysis for research purpose, especially in regard to training performance[116].

Mobile devices pose an alternative CCT platform, which, for reasons of cost, simplicity and portability, could be an important mode of delivery in the near future. 'Brain training' suites for the Nintendo DS handheld gaming device received some

empirical support[100,117], and numerous applications for mobile phones and tablets are now available, albeit trials using these two platforms have yet to be published. Video game consoles, particularly the Nintendo Wii, have been studied rigorously in recent years as a possible platform to provide mainly physical, balance and fine motor training, but results from several studies suggest that Wii-delivered CCT in older adults can be rather effective as well[85,114,118].

1.3.4 Training Content

After more than three decades of CCT research, it would be reasonable for the field to have identified what design features maximise transfer and focus on development and implementation of the most effective programs. Unfortunately, the field has not. A recent review of 39 CCT studies in healthy older adults[114], for example, identified 31 different programs. Although innovation is generally a positive feature, it is unclear whether the considerable investments in design and research of new CCT programs over the past decade are genuine improvements of the methods, or, to borrow a term from pharmaceutical industry, simply geared towards 'me too' software. Notwithstanding the specific differences from one program to another, the structure of CCT programs can be divided into three broad categories.

Single-domain CCT typically entails a small number of exercises (usually between one and five), which aim at one cognitive process or at closely related cognitive skills. Some popular examples include working memory training[109,119], visual processing speed training[120,121] and dual task training[103]. This kind of paradigms appeal to researchers because they offer a succinct insight into the malleability of a discrete cognitive ability[87,122], the neural mechanisms underlying training-induced adaptations[103,123-125], and the role such changes may have on other aspects of cognitive

performance[126]. Single-domain training does not tend to generalise beyond the trained domain[85], although some evidence for far transfer (i.e., effects that extend beyond the trained domain) does exist[86,110].

Along with single-domain programs[88], *Video games* were investigated for potential cognitive benefits in the elderly from the early days of CCT[89]. Video games are far from being a single construct with a clear scientific meaning[107], but the term is used interchangeably with others in the CCT literature. For the sake of clarity it is proposed to define 'video games' as interventions that were developed for general entertainment purposes (i.e., without a therapeutic intentions) and studied for their suitability as CCT. This design feature can arguably set video games apart from all other types of CCT, which typically have been designed in light of psychological or neuroscientific principles and intended for cognitive enhancement[96,114]. However, as long as the lack of regulatory environment for CCT continues, definitions may vary and the general misinterpretation of trial results in the media[107] is not likely to change. Nevertheless, video game training are often considered as a particular type of CCT, and a number of RCTs involving video games are reviewed with some caution in **Chapter 2**.

Finally, and probably the most prevalent type of CCT, *multi-domain* programs will entail two or more exercises targeting two or more cognitive domains. Multi-domain training is not to be confused with *multi-modal* training, as the latter term is used to describe programs that combine CT with other interventions, such as physical exercise and/or cognitive stimulation[85]. Some multi-domain CCT programs adjust training content to individual needs (based on individual performance), preferences

(based on pretraining questionnaires and/or manual selection) or following a prescribed program.

1.3.5 Delivery Methods

The third design feature that differentiates CCT programs describes the settings in which practice takes place. Traditionally, CCT studies have been conducted in a designated facility, usually the experimenter's laboratory. The experimenter's role in the training might me limited to mere technical facilitation of the program, or expended to provide guidance, strategy, metacognitive consideration and debriefing.

Studies involving self-administered training at-home begun to emerge in the late 1990s and are gaining increasing interest, in line with the increasing popularity of CCT via the internet. Some of the self-administered CCT studies provide initial training and follow-up (to provide technical assistance, ensure adherence, etc.[101,127]), whereas others merely provide access to the program and do not contact participants during the intervention period, similar to how home-based CCT usually works in the real world[128]. Finally, some programs for home use (such as Cogmed, CogniFit and Scientific Brain Training Pro) offer add-on case management systems that allow clinician to follow-up on trainees' progress and, in some cases, plan and modify their sessions.

1.4 Thesis Overview

Designing interventions that can effectively maintain cognition in the elderly is a priority in today's ageing world. Providing more opportunities for cognitive stimulation and improving cardiovascular health across the lifespan may help to extend recent reports of protective cohort effects [12,13,46,47]. These should be

complemented by interventions designed specifically for older adults at risk for ACRD, MCI and dementia. Numerous pharmacological and non-pharmacological interventions have been proposed, but most have failed to show efficacy in primary, secondary and tertiary prevention trials[129,130].

CT is not a panacea for cognitive ageing, but has accumulated an extensive body of evidence for efficacy on elders' cognitive performance. In addition, CCT is safe, highly prescriptive and inexpensive, which makes it a popular intervention in prevention-orientated trials. However, in order to advance the field, there is a need to address four critical issues, namely ending the 'brain training debate' by establishing a definitive answer to CCT efficacy (or lack thereof) of CCT, identifying the conditions that may facilitate generalisation and durability of any positive effects, measuring the dose-responsiveness of these effects and understanding the mechanisms of CCT-induced neuroplasticity[109]. This thesis aims to shed light on these four core issues.

Because systematic reviews of CCT in older adults tend to mix results from studies of very heterogeneous methodologies, a definitive review and meta-analysis of RCTs of CCT in healthy older adults has yet to be conducted. **Chapter 2** provides that first systematic review and meta-analysis of strictly defined RCTs of CCT in healthy older adults, quantifying not only the efficacy of CCT but also the moderating impact of the design features described in **Section 1.3** above.

Identifying the basic anatomy of efficacious CCT programs means the clinical applicability of CCT can be further investigated by finding the dose of training required to induce cognitive benefits. **Chapter 3** reports results from a randomised, active-controlled, longitudinal trial of CCT in healthy older adults (the Timecourse

Trial), whose main purpose was to measure the dose-responsiveness of key cognitive domains to CCT, as well as the timecourse by which such benefits may wane after training cessation.

Finally, **Chapter 4** tries to address the challenging problem of understanding the neural underpinnings of CCT efficacy. A subset of subjects from the Timecourse Trial underwent multi-modality Magnetic Resonance Imaging (MRI) scans before, during and after a course of CCT, and results are compared to the cognitive outcomes described in **Chapter 3**.

References

1. Hoyer WJ, Verhaeghen P. Memory Aging. In: Birren KW, Schaire EJ, eds. *Handbook of the psychology of aging (6th ed.)*. Amsterdam, Netherlands: Elsevier; 2006:209–232. doi:doi:10.1016/B978-012101264-9/50013-6.

2. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci*. 2004;5(2):87–96. doi:10.1038/nrn1323.

3. United Nations. *World Population Ageing 2009*. New York: United Nations; 2009. Available at: http://www.un.org/esa/population/publications/WPA2009/WPA2009_WorkingPaper.pdf.

4. World Health Organization, Alzheimers Disease International. *Dementia: a public health priority*. 2012. Available at: http://www.who.int/mental_health/publications/dementia_report_2012/en/.

5. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet*. 2009.

6. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002;31(2):285–293.

7. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819–828. doi:10.1016/S1474-4422(11)70072-2.

8. Carrillo MC, Brashear HR, Logovinsky V, et al. Can we prevent Alzheimer“s disease? Secondary ‘prevention’ trials in Alzheimer”s disease. *Alzheimers Dement*. 2013;9(2):123–131.e1. doi:10.1016/j.jalz.2012.12.004.

9. Lutz W, Sanderson W, Scherbov S. The coming acceleration of global population ageing. *Nature*. 2008;451(7179):716–719. doi:10.1038/nature06516.

10. Australian Bureau of Statistics. Australian Demographic Statistics, Sep 2012. 2013. Available at: http://www.abs.gov.au/AUSSTATS/subscriber.nsf/log?openagent&31010do002_201209.xls&3101.0&Data%20Cubes&4B8C05E5992DFA77CA257B3B00117985&0&Sep%202012&28.03.2013&Latest.

11. Anonymous. China's Achilles heel; Demography. *The Economist*. 2012;403(8781):53–54.

12. Christensen K, Thinggaard M, Oksuzyan A, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *Lancet*. 2013. doi:10.1016/S0140-6736(13)60777-1.

13. Matthews FE, Arthur A, Barnes LE, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. *Lancet*. 2013. doi:10.1016/S0140-6736(13)61570-6.

14. Vaupel JW, Loichinger E. Redistributing work in aging Europe. *Science*. 2006;312(5782):1911–1913. doi:10.1126/science.1127487.

15. Beddington J, Cooper CL, Field J, et al. The mental wealth of nations. *Nature*. 2008;455(7216):1057–1060. doi:10.1038/4551057a.

16. Brayne C. The elephant in the room - healthy brains in later life, epidemiology and public health. *Nat Rev Neurosci*. 2007;8(3):233–239. doi:10.1038/nrn2091.

17. Deary IJ, Corley J, Gow AJ, et al. Age-associated cognitive decline. *Br Med Bull*. 2009;92:135–152. doi:10.1093/bmb/ldp033.

18. Daffner KR. Promoting successful cognitive aging: a comprehensive review. *J Alzheimers Dis*. 2010;19(4):1101–1122. doi:10.3233/JAD-2010-1306.

19. Salthouse TA. When does age-related cognitive decline begin? *Neurobiol Aging*. 2009;30(4):507–514. doi:10.1016/j.neurobiolaging.2008.09.023.

20. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer‘s Association workgroups on diagnostic guidelines for Alzheimer’s disease. In: Vol 7. 2011:270–279. doi:10.1016/j.jalz.2011.03.008.

21. Skirbekk V, Loichinger E, Weber D. Variation in cognitive functioning as a refined approach to comparing aging across countries. *Proc Natl Acad Sci USA*. 2012;109(3):770–774. doi:10.1073/pnas.1112173109.

22. Bullock R. Mild cognitive impairment. *Psychiatry*. 2008;7(1):36–38. doi:10.1016/j.mppsy.2007.11.001.

23. Ylikoski R, Ylikoski A, Keskivaara P, Tilvis R, Sulkava R, Erkinjuntti T. Heterogeneity of cognitive profiles in aging: successful aging, normal aging, and individuals at risk for cognitive decline. *Eur J Neurol*. 1999;6(6):645–652.

24. Pusswald G, Moser D, Gleiß A, et al. Prevalence of mild cognitive impairment subtypes in patients attending a memory outpatient clinic-comparison of two modes of mild cognitive impairment classification. Results of the Vienna Conversion to Dementia Study. *Alzheimers Dement*. 2012. doi:10.1016/j.jalz.2011.12.009.

25. Wahl H-W, Heyl V, Drapaniotis PM, et al. Severe Vision and Hearing Impairment and Successful Aging: A Multidimensional View. *Gerontologist*. 2013. doi:10.1093/geront/gnt013.

26. Keage HAD, Banks S, Yang KL, Morgan K, Brayne C, Matthews FE. What sleep characteristics predict cognitive decline in the elderly? *Sleep Med*. 2012;13(7):886–892. doi:10.1016/j.sleep.2012.02.003.

27. Rockwood K, Wentzel C, Hachinski V, Hogan DB, MacKnight C, McDowell I. Prevalence and outcomes of vascular cognitive impairment. Vascular Cognitive Impairment Investigators of the Canadian Study of Health and Aging. *Neurology*. 2000;54(2):447–451.

28. Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9(1):119–128. doi:10.1016/S1474-4422(09)70299-6.

29. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer‘s Association workgroups on diagnostic guidelines for Alzheimer’s disease. In: Vol 7. 2011:280–292. doi:10.1016/j.jalz.2011.03.003.

30. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. *Lancet*. 2006;367(9518):1262–1270. doi:10.1016/S0140-6736(06)68542-5.

31. Petersen RC. Clinical practice. Mild cognitive impairment. *N Engl J Med*. 2011;364(23):2227–2234. doi:10.1056/NEJMcp0910237.

32. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement*. 2012;8(1):14–21. doi:10.1016/j.jalz.2011.01.002.

33. Thies W, Bleiler L, Alzheimer's Association. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2013;9(2):208–245. doi:10.1016/j.jalz.2013.02.003.

34. Petersen RC, Morris JC. Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol*. 2005;62(7):1160–3– discussion 1167. doi:10.1001/archneur.62.7.1160.

35. Jelic V, Kivipelto M, Winblad B. Clinical trials in mild cognitive impairment: lessons for the future. *J Neurol Neurosurg Psychiatr*. 2006;77(4):429–438. doi:10.1136/jnnp.2005.072926.

36. Whitehouse P, Brodaty H. Mild cognitive impairment. *Lancet*. 2006;367(9527):1979. doi:10.1016/S0140-6736(06)68880-6.

37. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. *World Psychiatry*. 2013;12(2):92–98. doi:10.1002/wps.20050.

38. World Health Organization. *ICD-10*. Who; 2004.

39. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2010;9(11):10–10. doi:10.1016/S1474-4422(10)70223-4.

40. McKhann GM, Knopman DS, Chertkow H, et al. 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. In: Vol 7. 2011:263–269. doi:10.1016/j.jalz.2011.03.005.

41. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry*. 1984;141(11):1356–1364.

42. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.

43. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566–572.

44. Valenzuela M, Esler M, Ritchie K, Brodaty H. Antihypertensives for combating dementia? A perspective on candidate molecular mechanisms and population-based prevention. *Transl Psychiatry*. 2012;2:e107. doi:10.1038/tp.2012.28.

45. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9(1):63–75.e2. doi:10.1016/j.jalz.2012.11.007.

46. Qiu C, Strauss von E, Bäckman L, Winblad B, Fratiglioni L. Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology*. 2013. doi:10.1212/WNL.0b013e318292a2f9.

47. Langa KM, Larson EB, Karlawish JH, et al. Trends in the prevalence and mortality of cognitive impairment in the United States: is there evidence of a compression of cognitive morbidity? *Alzheimers Dement*. 2008;4(2):134–144. doi:10.1016/j.jalz.2008.01.001.

48. Wimo A, Jönsson L, Bond J, Prince M, Winblad B, Alzheimer Disease International. The worldwide economic impact of dementia 2010. *Alzheimers Dement*. 2013;9(1):1–11.e3. doi:10.1016/j.jalz.2012.11.006.

49. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *N Engl J Med*. 2013;368(14):1326–1334. doi:10.1056/NEJMsa1204629.

50. Buschert V, Bokde ALW, Hampel H. Cognitive intervention in Alzheimer disease. *Nat Rev Neurol*. 2010;6(9):508–517. doi:10.1038/nrneurol.2010.113.

51. Wortmann M. Dementia: a global health priority - highlights from an ADI and World Health Organization report. *Alzheimers Res Ther*. 2012;4(5):40. doi:10.1186/alzrt143.

52. Australian Institute of Health and Welfare. *Dementia in Australia*. Canberra: AIHW; 2012.

53. Thal LJ. Prevention of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2006;20(3 Suppl 2):S97–9.

54. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement*. 2007;3(3):186–191. doi:10.1016/j.jalz.2007.04.381.

55. Vickland V, Morris T, Draper B, Low LF, Brodaty H. *Modelling the Impact of Interventions to delay the Onset of Dementia in Australia. (Canberra, 2012)*.

56. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. *Nat Rev Neurol*. 2011;7(3):137–152. doi:10.1038/nrneurol.2011.2.

57. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol*. 2006;5(9):735–741. doi:10.1016/S1474-4422(06)70537-3.

58. Almeida OP, Garrido GJ, Alfonso H, et al. 24-month effect of smoking cessation on cognitive function and brain structure in later life. *Neuroimage*. 2011;55(4):1480–1489. doi:10.1016/j.neuroimage.2011.01.063.

59. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008;300(9):1027–1037. doi:10.1001/jama.300.9.1027.

60. Lövdén M, Xu W, Wang H-X. Lifestyle change and the prevention of cognitive decline and dementia: what is the evidence? *Curr Opin Psychiatry*. 2013;26(3):239–243. doi:10.1097/YCO.0b013e32835f4135.

61. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychol Med*. 2006;36(4):441–454. doi:10.1017/S0033291705006264.

62. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508–2516. doi:10.1056/NEJMoa022252.

63. Marioni RE, van den Hout A, Valenzuela MJ, Brayne C, Matthews FE, MRC Cognitive Function and Ageing Study. Active cognitive lifestyle associates with cognitive recovery and a reduced risk of cognitive decline. *J Alzheimers Dis*. 2012;28(1):223–230. doi:10.3233/JAD-2011-110377.

64. Marioni RE, Valenzuela MJ, van den Hout A, Brayne C, Matthews FE, MRC Cognitive Function and Ageing Study. Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS ONE*. 2012;7(12):e50940. doi:10.1371/journal.pone.0050940.

65. Valenzuela M, Brayne C, Sachdev P, Wilcock G, Matthews F, Medical Research Council Cognitive Function and Ageing Study. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter

population-based cohort. *Am J Epidemiol*. 2011;173(9):1004–1012. doi:10.1093/aje/kwq476.

66. Krueger KR, Wilson RS, Kamenetsky JM, Barnes LL, Bienias JL, Bennett DA. Social engagement and cognitive function in old age. *Exp Aging Res*. 2009;35(1):45–60. doi:10.1080/03610730802545028.

67. Valenzuela MJ, Matthews FE, Brayne C, et al. Multiple biological pathways link cognitive lifestyle to protection from dementia. *Biol Psychiatry*. 2012;71(9):783–791. doi:10.1016/j.biopsych.2011.07.036.

68. Suo C, León I, Brodaty H, et al. Supervisory experience at work is linked to low rate of hippocampal atrophy in late life. *Neuroimage*. 2012;63(3):1542–1551. doi:10.1016/j.neuroimage.2012.08.015.

69. Cagney KA, Lauderdale DS. Education, wealth, and cognitive function in later life. *J Gerontol B Psychol Sci Soc Sci*. 2002;57(2):P163–72.

70. Schmidt FL. The Role of General Cognitive Ability and Job Performance: Why There Cannot Be a Debate. *Human Performance*. 2002;15(1-2):187–210. doi:doi: 10.1080/08959285.2002.9668091.

71. Rocca WA, Petersen RC, Knopman DS, et al. Trends in the incidence and prevalence of Alzheimer's disease, dementia, and cognitive impairment in the United States. *Alzheimers Dement*. 2011;7(1):80–93. doi:10.1016/j.jalz.2010.11.002.

72. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. *Neurology*. 2009;73(5):356–361. doi:10.1212/WNL.0b013e3181b04ae3.

73. Jefferson AL, Gibbons LE, Rentz DM, et al. A life course model of cognitive activities, socioeconomic status, education, reading ability, and cognition. *J Am Geriatr Soc*. 2011;59(8):1403–1411. doi:10.1111/j.1532-5415.2011.03499.x.

74. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006–1012. doi:10.1016/S1474-4422(12)70191-6.

75. Tucker AM, Stern Y. Cognitive reserve in aging. *Curr Alzheimer Res*. 2011;8(4):354–360.

76. EClipSE Collaborative Members, Brayne C, Ince PG, et al. Education, the brain and dementia: neuroprotection or compensation? *Brain*. 2010;133(Pt 8):2210–2216. doi:10.1093/brain/awq185.

77. Prince M, Acosta D, Ferri CP, et al. Dementia incidence and mortality in middle-income countries, and associations with indicators of cognitive reserve: a 10/66 Dementia Research Group population-based cohort study. *Lancet*. 2012;380(9836):50–58. doi:10.1016/S0140-6736(12)60399-7.

78. Yates FA. *The Art Of Memory*. Random House; 2011.

79. Sarma G. The Art of Memory and the Growth of the Scientific Method. *arXiv preprint arXiv:13070254*. 2013. Available at: http://arxiv.org/pdf/1307.0254v2.pdf.

80. Spaulding WD, Storms L, Goodrich V, Sullivan M. Applications of experimental psychopathology in psychiatric rehabilitation. *Schizophr Bull*. 1986;12(4):560–577.

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

82. Hoyer WJ, Labouvie GV, Baltes PB. Modification of Response Speed Deficits and Intellectual Performance in the Elderly. *Human Development*. 1973;16(3):233–242.

83. Labouvie-Vief G, Gonda JN. Cognitive strategy training and intellectual performance in the elderly. *J Gerontol*. 1976;31(3):327–332.

84. Plemons JK, Willis SL, Baltes PB. Modifiability of fluid intelligence in aging: a short-term longitudinal training approach. *J Gerontol*. 1978;33(2):224–231.

85. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: a review and future directions. *Neuropsychol Rev*. 2009;19(4):504–522. doi:10.1007/s11065-009-9119-9.

86. Zelinski EM. Far transfer in cognitive training of older adults. *Restor Neurol Neurosci*. 2009;27(5):455–471. doi:10.3233/RNN-2009-0495.

87. Ball K, Sekuler R. A specific and enduring improvement in visual motion discrimination. *Science*. 1982;218(4573):697–698.

88. Ball K, Sekuler R. Improving visual perception in older observers. *J Gerontol*. 1986;41(2):176–182.

89. Salthouse TA, Somberg BL. Skilled performance: Effects of adult age and experience on elementary processes. *Journal of Experimental Psychology: General*. 1982;111(2):176–207. doi:doi:10.1037/0096-3445.111.2.176.

90. Mowszowski L, Batchelor J, Naismith SL. Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *Int Psychogeriatr*. 2010;22(4):537–548. doi:10.1017/S1041610209991748.

91. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry*. 2011;168(5):472–485. doi:10.1176/appi.ajp.2010.10060855.

92. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive

impairment. *Cochrane Database Syst Rev*. 2011;(1):CD006220. doi:10.1002/14651858.CD006220.pub2.

93. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev*. 2013;6:CD003260. doi:10.1002/14651858.CD003260.pub2.

94. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev*. 2003;(4):CD003260. doi:10.1002/14651858.CD003260.

95. Gates N, Valenzuela M. Cognitive exercise and its role in cognitive function in older adults. *Curr Psychiatry Rep*. 2010;12(1):20–27. doi:10.1007/s11920-009-0085-y.

96. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*. 2012;37(1):43–76. doi:10.1038/npp.2011.251.

97. Wykes T, Spaulding WD. Thinking about the future cognitive remediation therapy--what works and could we do better? *Schizophr Bull*. 2011;37 Suppl 2:S80–90. doi:10.1093/schbul/sbr064.

98. Hoffmann TC, Erueti C, Glasziou PP. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *BMJ*. 2013;347.

99. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271–2281.

100. Nouchi R, Taki Y, Takeuchi H, et al. Brain training game improves executive functions and processing speed in the elderly: a randomized controlled trial. *PLoS ONE*. 2012;7(1):e29676. doi:10.1371/journal.pone.0029676.

101. Mahncke HW, Connor BB, Appelman J, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci USA*. 2006;103(33):12523–12528. doi:10.1073/pnas.0605194103.

102. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) Trial: A Randomized Controlled Trial to Enhance Cognitive Function in Older Adults. *JAMA Intern Med*. 2013;173(9):797–804. doi:10.1001/jamainternmed.2013.189.

103. Anguera JA, Boccanfuso J, Rintoul JL, et al. Video game training enhances cognitive control in older adults. *Nature*. 2013;501(7465):97–101. doi:Letter.

104. Miller KJ, Dye RV, Kim J, et al. Effect of a computerized brain exercise program on cognitive performance in older adults. *Am J Geriatr Psychiatry*.

2013;21(7):655–663. doi:10.1016/j.jagp.2013.01.077.

105. Bozoki A, Radovanovic M, Winn B, Heeter C, Anthony JC. Effects of a computer-based cognitive exercise program on age-related cognitive decline. *Arch Gerontol Geriatr*. 2013;57(1):1–7. doi:10.1016/j.archger.2013.02.009.

106. Lee Y, Lee C-R, Hwang B. Effects of Computer-aided Cognitive Rehabilitation Training and Balance Exercise on Cognitive and Visual Perception Ability of the Elderly TI . *Journal of Physical Therapy Science*. 2012;24(9):885–887.

107. Bavelier D, Green CS, Han DH, Renshaw PF, Merzenich MM, Gentile DA. Brains on video games. *Nat Rev Neurosci*. 2011;12(12):763–768. doi:10.1038/nrn3135.

108. Kurz AF, Leucht S, Lautenschlager NT. The clinical significance of cognition-focused interventions for cognitively impaired older adults: a systematic review of randomized controlled trials. *Int Psychogeriatr*. 2011:1–12. doi:10.1017/S1041610211001001.

109. Jaeggi SM, Buschkuehl M, Jonides J, Shah P. Short- and long-term benefits of cognitive training. *Proc Natl Acad Sci USA*. 2011;108(25):10081–10086. doi:10.1073/pnas.1103228108.

110. Cheng Y, Wu W, Feng W, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. *BMC Med*. 2012;10:30. doi:10.1186/1741-7015-10-30.

111. Buschert VC, Friese U, Teipel SJ, et al. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer's disease: a pilot study. *J Alzheimers Dis*. 2011;25(4):679–694. doi:10.3233/JAD-2011-100999.

112. Buschert VC, Giegling I, Teipel SJ, et al. Long-term observation of a multicomponent cognitive intervention in mild cognitive impairment. *J Clin Psychiatry*. 2012;73(12):e1492–8. doi:10.4088/JCP.11m07270.

113. Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychol Aging*. 1992;7(2):242–251.

114. Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: a systematic review. *PLoS ONE*. 2012;7(7):e40588. doi:10.1371/journal.pone.0040588.

115. Jak AJ, Seelye AM, Jurick SM. Crosswords to computers: a critical review of popular approaches to cognitive enhancement. *Neuropsychol Rev*. 2013;23(1):13–26. doi:10.1007/s11065-013-9226-5.

116. Sternberg DA, Ballard K, Hardy JL, Katz B, Doraiswamy PM, Scanlon M. The largest human cognitive performance dataset reveals insights into the effects of lifestyle factors and aging. *Front Hum Neurosci*. 2013;7:292.

doi:10.3389/fnhum.2013.00292.

117. McDougall S, House B. Brain training in older adults: evidence of transfer to memory span performance and pseudo-Matthew effects. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2012;19(1-2):195–221. doi:10.1080/13825585.2011.640656.

118. Maillot P, Perrot A, Hartley A. Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. *Psychol Aging*. 2012;27(3):589–600. doi:10.1037/a0026268.

119. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. *Nat Neurosci*. 2004;7(1):75–79. doi:10.1038/nn1165.

120. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults. *PLoS ONE*. 2013;8(5):e61624. doi:10.1371/journal.pone.0061624.

121. Edwards JD, Wadley VG, Myers RES, Roenker DL, Cissell GM, Ball KK. Transfer of a speed of processing intervention to near and far cognitive functions. *Gerontology*. 2002;48(5):329–340.

122. Brehmer Y, Westerberg H, Bäckman L. Working-memory training in younger and older adults: training gains, transfer, and maintenance. *Front Hum Neurosci*. 2012;6:63. doi:10.3389/fnhum.2012.00063.

123. Berry AS, Zanto TP, Clapp WC, et al. The influence of perceptual training on working memory in older adults. *PLoS ONE*. 2010;5(7):e11537. doi:10.1371/journal.pone.0011537.

124. Lövdén M, Schaefer S, Noack H, et al. Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol Aging*. 2012;33(3):620.e9–620.e22. doi:10.1016/j.neurobiolaging.2011.02.013.

125. Brehmer Y, Rieckmann A, Bellander M, Westerberg H, Fischer H, Bäckman L. Neural correlates of training-related working-memory gains in old age. *Neuroimage*. 2011;58(4):1110–1120. doi:10.1016/j.neuroimage.2011.06.079.

126. Jaeggi SM, Buschkuehl M, Jonides J, Perrig WJ. Improving fluid intelligence with training on working memory. *Proc Natl Acad Sci USA*. 2008;105(19):6829–6833. doi:10.1073/pnas.0801268105.

127. Smith GE, Housen P, Yaffe K, et al. A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study. *J Am Geriatr Soc*. 2009;57(4):594–603. doi:10.1111/j.1532-5415.2008.02167.x.

128. Owen AM, Hampshire A, Grahn JA, et al. Putting brain training to the test. *Nature*. 2010;465(7299):775–778. doi:10.1038/nature09042.

129. Middleton LE, Yaffe K. Targets for the prevention of dementia. *J Alzheimers Dis*. 2010;20(3):915–924. doi:10.3233/JAD-2010-091657.

130. Andrieu S, Coley N, Aisen P, et al. Methodological issues in primary prevention trials for neurodegenerative dementia. *J Alzheimers Dis*. 2009;16(2):235–270. doi:10.3233/JAD-2009-0971.

Chapter 2: Dissecting the Anatomy of Computerised Cognitive Training: A Systematic Review and Meta-Analysis

2.1 Introduction

2.1.1 Rationale

Human adult ageing is associated with a gradual process of age-related cognitive decline (ARCD). Further deterioration in cognition can lead to mild cognitive decline (MCI) and dementia, whose prevalence in adults over 65 years of age is estimated at 20% and 15%, respectively[1] (see **Chapter 1** for a detailed discussion of limitations in MCI nosology and epidemiology). Given strong links between engagement in cognitively stimulating activities and enhanced late-life cognition and reduced risk of MCI and dementia[2-4] (see **Chapter 1**), there has been growing interest in cognition-focused interventions that may attenuate ARCD and help maintain cognitive performance in older adults. Arguably, the most studied intervention is cognitive training (CT), which involves structured practice on standardised cognitively challenging tasks[5]. Despite a wealth of studies linking CT to various cognitive benefits and neuroplastic changes in older adults[6-8], the current evidence base is methodologically heterogeneous and results inconsistent[5].

Recent years has seen a sharp increase in the popularity of computer-assisted cognitive training (CCT) among researchers and the public alike. CCT has several advantages over traditional CT methods, including more visually appealing interfaces, efficient and scalable delivery and the ability to constantly adapt training content and

difficulty to individual performance[8-10]. However, as in the case of traditional CT, the CCT literature suffers from several limitations, including lack of adequate control groups, poor study designs, lack of longitudinal follow-ups, unclear relevance of study outcomes to everyday performance and inconsistent methodology (in terms of e.g., program design, dose and outcome measures). Together, these issues have made a synthetic evaluation of the literature challenging and impeded translation of trial results to clinical practice[5,7,8,11-14].

To date the efficacy of CCT on cognitive performance in healthy older adults has yet to be comprehensively addressed in a systematic review. Three recent reviews[5,13,14] attempted to pool outcomes from different cognition-based interventions (CT, CCT, and non-CT methods such as cognitive stimulation) and, unsurprisingly, reached inconclusive results. By contrast, a recent systematic review of CCT in healthy older adults[8] refrained from a quantitative meta-analysis, citing the degree of methodological inconsistencies between studies.

A balance between pooling inherently different studies into the same analysis[5] versus excess conservatism[8] may therefore be required in order to make new insights about the efficacy of CCT. One approach is to take advantage of more recent meta-analytic technology that allows flexible testing of not only overall efficacy claims, but also identification of moderating efficacy factors[15]. In the context of meta-analysis, moderating factors are design features of the included RCTs that can influence their effect size estimate.

2.1.2 Objectives

In healthy older adults, we aimed to:

1) Evaluate the efficacy of RCTs of CCT on different cognitive outcomes;
2) Test the moderating effects of several key design features;
3) Assess the nature and quality of RCT evidence; and
4) Suggest recommendations for future CCT research based on these findings.

2.2 Methods

The PRISMA guidelines for design, conduct and reporting of meta-analyses were implemented[16].

2.2.1 Eligibility Criteria

Types of studies: Published, peer-reviewed articles reporting results from randomised controlled trials (RCTs) studying the effects of CCT on one or more cognitive outcomes in healthy older adults.

Types of participants: Mean participant age ≥60 years and lack of any major cognitive, neurological, psychiatric and/or sensory impairments. Studies with MCI as inclusion criterion were excluded as cognitive performance in this population may vary substantially and conversion from MCI to dementia during the trial period could not be ruled out.

Types of interventions: Trials comparing the effects of ≥4 hours of extended practice on standardised computerised tasks with clear cognitive rationale[17,18], or immersive technologies or video games, administered on personal computers, mobile devices or gaming consoles, versus active or passive control condition. Lab-specific interventions that do not involve interaction with a computer (e.g., overhead projectors and simulators) were excluded from the review.

Types of outcome measures: Performance in one or more cognitive tests that were not included in the training program (i.e., untrained), administered both before and after training. This review is limited to change in performance from baseline to immediately post-training on tests of memory, working memory (WM), processing speed, attention, language, visuospatial skills and executive functions. Both primary and secondary outcomes were included. Long-term outcomes, subjective measures (e.g., questionnaires), non-cognitive (e.g., mood, physical) and activities of daily living (ADLs) measurements were excluded from the analysis.

2.2.2 Information Sources and Search

Studies were identified by searching on all the databases included in ISI Web of Knowledge using the search terms *"cognitive training" OR "brain training" OR "memory training" OR "attention training" OR "reasoning training" OR "extended practice"*, and by scanning reference lists of articles and reviews. No limits were applied for publication dates and non-English papers were translated. This search was conducted on 13 August 2013. One additional study published in September 2013[19] and results from the Timecourse Trial (**Chapter 3**) were included as well. The candidate developed and conducted the search.

2.2.3 Study Selection

Eligibility assessment was performed in three stages. First, the candidate scanned all records and excluded ineligible abstracts based on title, abstract and type of record. All records that were not peer-reviewed published articles (particularly conference abstracts) were excluded at this point as well. Second, the candidate and an additional lab member independently scanned the remaining full-text articles for eligibility, and

determined inclusion by means of consensus. Finally, the candidate's supervisor assessed eligibility of selected studies.

2.2.4 Data Collection and Coding

Coding of outcomes measures into cognitive domains and data extraction was done based on accepted neuropsychological categorisation[20] or by consensus between the candidate and an additional lab member. Data was entered into Comprehensive Meta Analysis (CMA[21], Biostat Inc., Englewood, NJ) Version 2.2.064.

Data from most studies were entered as means and standard deviations (SD) of the CCT and control groups at baseline and follow-up. A conservative pre-post correlation of 0.6 was selected and preset for all analyses. When studies presented data for both active and passive control groups, only the active control group was used as a comparison to CCT. In a few instances, data were entered as post-training mean change[19,22,23], Hedge's g with 95% confidence interval (CI)[24] or raw mean difference with 95% CI[25]. CMA allows for each of these different study outcomes to be flexibly entered into the model.

When data could not be extracted from study reports, we contacted the authors requesting raw data. We contacted 15 authors, of which 12 provided raw data or methodological clarifications, after which four papers were excluded due to ineligibility[26-29]. Of the three papers whose authors did not respond or provided the requested data, two were excluded[30,31], and one was included after reviewing the study protocol in the clinical trials registry[23].

Data from two studies received different treatment. First, Wolinsky et al[32] presented data from four groups, namely: 1) speed of processing (SOP) training on-site, 2) same

intervention with long term booster training, 3) SOP training at-home, and 4) an active on-site control group. Since groups 1 and 2 received the same intervention between baseline and immediate post-training assessment, data (means and SD) from these groups were combined using the formulae suggested by Higgins and Green[33] and compared to group 4. Data from group 3 was omitted from the analysis due to lack of a matching at-home control group. Second, Colzato et al[34] used the same CCT in two groups genotyped for the brain-derived neurotrophic factor (BDNF) Val[66]Met polymorphism, compared to genotype-matched (Val/Val or Met-/ carriers) control groups. Data from each pair of groups therefore were treated as different studies.

2.2.5 Data Items

Information extracted from each included trial included:

1. Characteristics of trial participants: age, sex (% males), MMSE score (when reported).
2. Intervention details: type of CCT (multidomain, speed of processing (SOP), WM training, video games), delivery (centre- or home-based), total dose (in hours), number of sessions, session length (in minutes), session frequency (per week).
3. Control condition: active (control intervention) or passive (wait-list or no-contact) control.
4. Outcomes: test, subtest/phase (when applicable), targeted domain, form of administration (computerised or paper-based), delayed or immediate recall (for memory outcome).
5. Study design: type of control (active or passive control), blinding (unblinded, participant-blinded, assessor-blinded, double-blind).

2.2.6 Study Quality of Individual Studies

The Physiotherapy Evidence Database (PEDro) scale was used to assess study quality. PEDro is a 11-item scale designed to assess the methodological quality and reporting of RCTs, and is reliable for rating trials of non-pharmacological interventions[35]. It should be noted, however, that since one of the PEDro items is 'blinding of therapist who administered the therapy', is yet to be implemented in any RCT of CCT, then the maximum score for studies in this review was 10. Two independent assessors performed PEDro assessment for each study, and were subsequently reviewed by the candidate.

2.2.7 Summary Measures and Planned Methods of Analysis

All analyses were conducted using CMA by computing standardised mean difference (SMD) between CCT and control groups on each cognitive outcome measure, based on a random-effects model with 95% confidence intervals (CI). SMD was calculated as the difference in gain from baseline to immediately post-training assessment between the CCT and control group. When studies reported several outcome measures from the same cognitive domain, all measures of the same domain were automatically combined into one outcome measure, a standard feature of CMA. The I^2 statistic was used to determine the degree of heterogeneity between studies in a particular meta-analysis[36]. I^2 values of 25%, 50% and 75% imply small, medium and large heterogeneity, respectively[36]. Forest plots were used to examine the distribution of SMDs and to detect outliers.

Two types of analyses were planned and conducted:

Efficacy: To estimate the overall efficacy of CCT, SMDs were calculated separately for each study and pooled by domain regardless of heterogeneity. All cognitive outcomes were analysed regardless of classifications as primary or secondary. Significance was defined at $p<0.05$.

Moderators of efficacy: To potentially explain between-study variability and which design elements may moderate observed efficacy, we performed subgroup meta-analyses for each domain using following moderators discussed in **Chapter 1**:

1. CCT types: Multidomain, speed of processing (SOP) training, WM training, video games.
2. CCT practice: delivery, dose, session length, session frequency.
3. Study design: control condition, nature of blinding, test administration (computerised or paper-and-pencil).
4. Study quality: PEDro score.

A formal moderator test was performed using the Q-statistic, which is based on a mixed effects model with 95% CI, and tests for heterogeneity between sub-groups of studies. Under this model, within-subgroup heterogeneity is calculated using random effect, whereas between-group heterogeneity is based on fixed-effect model. Based on prior practice, between sub-group heterogeneity is defined as $p<0.1$[37].

Planned meta-regression analyses were performed to examine SMDs against dose, session length, session frequency and PEDro scores. Only one study[38] provided a total dose of more than 40 hours and was therefore excluded from dose analyses.

2.2.8 Risk of Bias Across Studies and Additional Analyses

As this review was limited to published results, it is important to test whether publication bias or selective reporting of results might have affected the findings. Following previous recommendations[39], we visually inspected funnel plots based on SMDs and standard error for every cognitive domain using CMA, and tested possible funnel plots asymmetries using Egger's Test of the Intercepts[40]. When possible publication bias was detected (1-tailed $p<0.1$), intercepts and 95% CI were calculated using CMA.

2.3 Results

2.3.1 Study Selection and Characteristics

Figure 2.1 presents a flowchart for study selection. Of the 37 studies included in this review, 22 were obtained from the original search and 15 were added from our own manual search. Overall, the 37 studies encompassed 4,310 participants and provided 344 effect sizes (see **Table 2.1**). All studies were randomised controlled trials (RCTs) with at least one CCT and one control arm. 30 different CCT programs were identified, with doses (i.e., total training time) ranging from 4[41] to 60[42] hours.

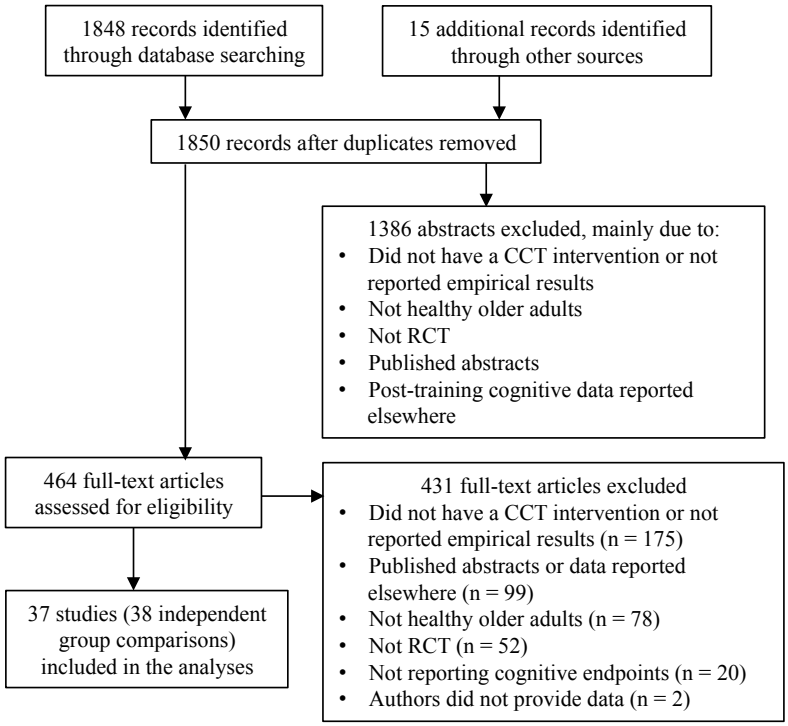


Figure 2.1: Flow diagram for the search and inclusion of studies in this review

Table 2.1: Study characteristics

	Study demographics[a]				Intervention design							Study design and quality		
Study name	N	Age	Sex[b]	MMSE	CCT type	Delivery	Program	Dose	Sess.	Length	S/wk	Control	Design	PEDro
Ackerman 2010[43]	78	60.7	69		Multidomain	Home	Wii Big Brain Academy	20	20	60	5	Active	Unblinded	3
Anderson 2013[44]	67	63.0	41.8	27.4	Multidomain	Home	Posit Brain Fitness	40	40	60	5	Active	Assessor-Blind	6
Anguera 2013[19]	31	66.8		≥26	Video Game	Home	In-house program ('NeuroRacer')	12	12	60	3	Active	Subject-Blind	6
Ball 2002[45]	1398	73.6	24	27.3	Speed of Processing	Centre	Speed of Processing	11	10	67	2	Passive	Assessor-Blind	9
Barnes 2013[46]	63	73.9	39.7	28.4[c]	Multidomain	Home	Posit Brain Fitness + Insight	36	36	60	3	Active	Double	9
Basak 2008[47]	34	69.6	25.7	29.3	Video Game	Centre	Rise of Nations	24	15	120	3	Passive	Unblinded	5
Boot 2013[38]	41	72.5	39.9	29	Multidomain	Home	Brain Age 2 (Nintendo DS)	60	60	60	5	Passive	Unblinded	7
Bottiroli 2009[48]	44	66.2		27.6	Multidomain	Centre	Neuropsychological Training software	6	3	90	1	Passive	Unblinded	6
Bozoki 2013[49]	60	68.9	41.6	27.3	Multidomain	Home	In-house program ('My Better Mind')	30	30	60	5	Active	Subject-Blind	6
Brehmer 2011[50]	24	63.6	50.0		Working memory	Home	Cogmed	10	25	25	5	Active	Unblinded	8
Brehmer 2012[51]	45	63.8	55.4		Working memory	Home	Cogmed	9	23	26	4	Active	Double	8
Buschkuehl 2008[52]	39	80.0	41.0		Multidomain	Centre	In-house program	18	24	45	2	Active	Unblinded	5
Colzato 2011[34]	20	53.3	54.3	28.8	Multidomain	Home	In-house program	25	50	30	7	Active	Unblinded	4
Dahlin 2008[53]	29	68.3	37.9	28.8	Working memory	Centre	In-house program	11	15	45	3	Passive	Unblinded	6
Edwards 2002[54]	97	73.7	43.3		Speed of Processing	Centre	Speed of Processing	10	10	60	2	Passive	Unblinded	5
Edwards 2005[55]	126	75.6		28.1	Speed of Processing	Centre	Speed of Processing	10	10	60	2	Active	Unblinded	6
Goldstein 1997[56]	22	77.7			Video Game	Home	Tetris	31				Passive	Unblinded	5

Table 2.1: Study characteristics

	Study demographics[a]				Intervention design							Study design and quality		
Study name	N	Age	Sex[b]	MMSE	CCT type	Delivery	Program	Dose	Sess.	Length	S/wk	Control	Design	PEDro
Lampit 2013[57]	77	72.1	32.2	28.0	Multidomain	Centre	Cogpack	36	36	60	3	Active	Double	9
Lee 2012[58]	30	0.0	46.7	27.0	Speed of Processing	Centre	RehaCom	9	18	30	3	Active	Unblinded	4
Legault 2011[59]	36	75.7	58.5	28.5[c]	Multidomain Working memory	Centre	In-house program	18	24	44	2	Active	Assessor-Blind	8
Mahncke 2006[24]	123	70.9	50.0	≥24	Multidomain	Home	Posit Brain Fitness (prototype)	40	40	60	5	Active	Assessor-Blind	8
Maillot 2012[22]	30	73.5		28.0	Multidomain	Centre	Exergames (Nintendo Wii)	24	24	60	2	Passive	Unblinded	5
McAvinue 2013[60]	36	70.4	36.1	28.1	Working memory	Home	In-house program	36	36	60	3	Active	Unblinded	3
Miller 2013[61]	69	81.9	32.3	28.0	Multidomain	Home	Dakim's Brain Fitness	15	40	23	5	Passive	Unblinded	6
Nouchi 2012[23]	28	69.1		28.5	Multidomain	Home	Nintendo Brain Age	5	20	15	5	Active	Double	8
Peretz 2011[62]	155	67.8	38.0	29.0	Multidomain	Home	CogniFt	16	39	25	3	Active	Double	10
Rasmusson 1999[63]	24	79.2		27.8	Multidomain	Centre	Colorado Neuropsychology Tests	14	9	90	1	Passive	Unblinded	6
Richmond 2011[64]	40	66.0	20.0	29.0	Working memory	Home	In-house program	10	20	30	4	Active	Unblinded	6
Shatil 2013[65]	64	80.5	32.3	≥24	Multidomain	Centre	CogniFit	32	48	40	3	Active	Unblinded	5
Simpson 2012[66]	34	62.3	47.1	≥27	Multidomain	Home	mybraintrainer.com	7	21	20	7	Active	Unblinded	7
Smith 2009[25]	487	75.3	47.6	29.2	Multidomain	Home	Posit Brain Fitness	40	40	60	5	Active	Double	10
Stern 2011[67]	40	66.3	46.0		Video Game	Centre	Space Fortress	36	36	60	3	Passive	Unblinded	8
van Muijden 2012[68]	72	67.6	55.6	28.8	Multidomain	Home	In-house program	25	49	30	7	Active	Subject-Blind	7

Table 2.1: Study characteristics

	Study demographics[a]				Intervention design							Study design and quality		
Study name	N	Age	Sex[b]	MMSE	CCT type	Delivery	Program	Dose	Sess.	Length	S/wk	Control	Design	PEDro
Vance et al 2007[69]	159	75.1	52.2	28.6	Speed of Processing	Centre	Speed of Processing	10	10	60	1	Active	Unblinded	4
von Bastian 2013[70]	57	68.5	59.6	≥25	Working memory	Home	In-house program	16	20	27	5	Active	Double	8
Wang 2011[41]	52	64.2	32.7	28.4	Video Game	Centre	In-house program	4	5	45	1	Active	Subject-Blind	6
Wolinsky 2011[32]	456	61.9	39.1		Speed of Processing	Centre	Posit On the Road	10	5	120	1	Active	Double	8

[a] For the whole sample; [b] % males; [c] converted from the Modified Mental State Exam (3MSE, 1-100 scale) to MMSE 1-30 scale,

2.3.2 Meta-Analysis of Memory Outcomes

Efficacy on Memory. Figure 2.2 shows effects for the $k = 25$ studies comparing pretest–posttest gains between CCT and control groups on all *memory* measures, excluding WM (N CCT = 1,654, mean sample size = 66; N controls = 1,614, mean sample size = 65). 19 studies reported more than one memory outcomes, which were combined into one effect size per study. The combined effect size was small but significant (SMD = 0.28, 95% CI [0.09, 0.47], $p<0.01$). The heterogeneity between studies was large and significant, $I^2 = 78.99\%$, $p<0.01$. The funnel plot showed considerable asymmetry towards the left of the funnel (Egger's intercept = 1.23, 95% CI [-0.18, 2.63], $p=0.04$, see Figure 2.3), suggesting possible under-reporting of positive outcomes. Table 3.2. presents training efficacy by memory sub-domains.

Study name	Outcome	Std diff in means	Standard error	Variance	Lower limit	Upper limit	p-Value
Barnes et al (2013)	Combined	-0.236	0.253	0.064	-0.732	0.260	0.350
Boot et al (2013)	Combined	-0.138	0.321	0.103	-0.767	0.491	0.668
Rasmusson et al (2010)	Combined	-0.104	0.424	0.180	-0.936	0.728	0.807
Dahlin et al (2008)	Combined	-0.079	0.375	0.141	-0.814	0.656	0.834
Legault et al (2011)	Combined	-0.059	0.351	0.123	-0.746	0.628	0.866
Simpson et al (2012)	Combined	-0.057	0.367	0.135	-0.778	0.663	0.876
Brehmer et al (2012)	RAVLT	-0.045	0.302	0.091	-0.636	0.547	0.883
Bozoki et al (2013)	Combined	-0.017	0.259	0.067	-0.525	0.492	0.949
Ball et al (2002)	Combined	-0.009	0.053	0.003	-0.114	0.096	0.871
Miller et al (2013)	Combined	0.034	0.233	0.054	-0.423	0.491	0.885
Vance et al (2007)	Combined	0.061	0.159	0.025	-0.251	0.372	0.703
Stern et al (2011)	Combined	0.104	0.321	0.103	-0.525	0.734	0.745
Edwards et al (2002)	Combined	0.110	0.210	0.044	-0.302	0.522	0.601
Buschkuehl et al (2008)	Combined	0.111	0.251	0.063	-0.381	0.602	0.659
Smith et al (2009)	Combined	0.142	0.091	0.008	-0.035	0.320	0.117
Mahncke et al (2006)	RBANS Gobal Auditory Memory/Attention Score	0.184	0.634	0.402	-1.058	1.426	0.771
Peretz et al (2011)	Combined	0.214	0.183	0.034	-0.145	0.574	0.243
Richmond et al (2011)	Combined	0.263	0.322	0.104	-0.369	0.895	0.415
Basak et al (2008)	Visual STM	0.363	0.323	0.104	-0.270	0.996	0.261
Lampit et al (2013)	Combined	0.440	0.233	0.054	-0.017	0.896	0.059
McAvinue et al (2013)	Combined	0.527	0.341	0.116	-0.141	1.195	0.122
Brehmer et al (2011)	RAVLT	0.561	0.426	0.181	-0.273	1.395	0.187
Shatil (2012)	Global Visual Memory	0.726	0.263	0.069	0.211	1.241	0.006
Bottiroli et al (2009)	Combined	1.443	0.393	0.154	0.673	2.212	0.000
Anderson et al (2013)	Memory for Words (WJ-III Auditory STM) -SS	3.862	0.414	0.171	3.051	4.673	0.000
		0.282	0.098	0.010	0.090	0.475	0.004

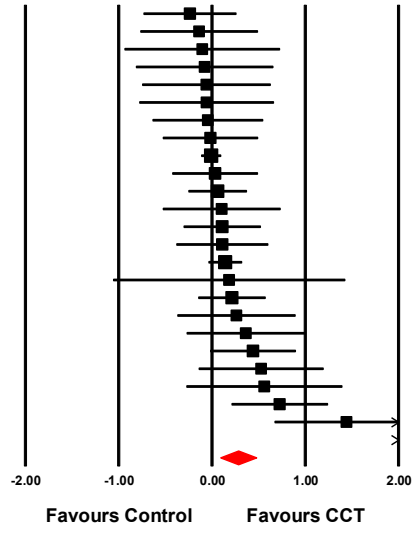


Figure 2.2: Forest plot for effects on memory based on all studies, rank ordered by SMD.

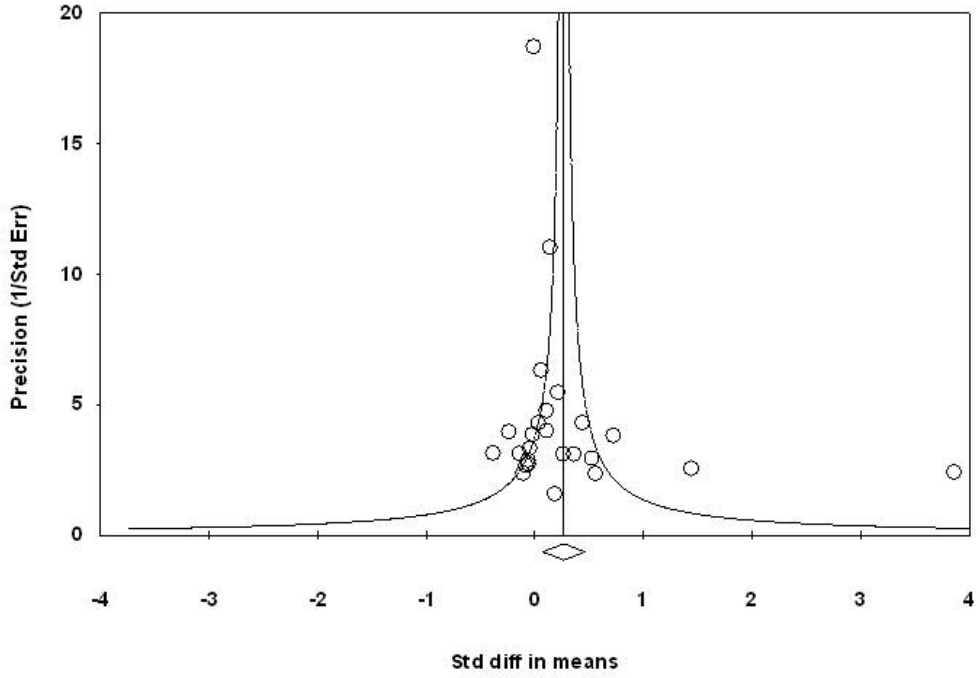


Figure 2.3: Funnel plot of precision by SMD for studies reporting memory outcomes

Memory subomain		All outcome for subdomain	Immediate recall	Delayed recall
Verbal memory	*k*	20	14	8
	SMD (95% CI)	0.22 (0–0.45)	0.26 (-0.03–0.55)	0.10 (-0.04–0.24)
	I^2	80.12%**	86.29%**	4.45%
Non-verbal memory	*k*	11	8	5
	SMD (95% CI)	0.37* (0.7–0.66)	0.38* (0.01–0.75)	0.36 (-0.01–0.73)
	I^2	75.82%**	79.1%**	65.58%*

Table 3.2.: Effect sizes for memory subdomains (all studies)
* $p < 0.05$. ** $p < 0.01$.

Moderators of CCT efficacy on memory outcomes. Figure 2.4 presents subgroup analysis of memory outcomes by type of CCT. Only multidomain CCT produced significant effects of medium size (k=14, SMD = 0.43, 95% CI [0.07, 0.79], p=0.02, I^2=86.95%, p=0.02). There were no significant effects on memory for SOP training (k=3, SMD = 0.004, 95% CI [-0.09, 0.09], p=0.93, I^2=0%, p=0.80), video games (k=2, SMD = 0.23, 95% CI [-0.21, 0.68], p=0.31, I^2=0%, p=0.57) and WM training (k=6, SMD = 0.17, 95% CI [-0.10, 0.45], p=0.22, I^2=0%, p=0.64).

In addition, a significant formal test for moderator effect was found for training type ($Q(3)=6.46$, $p=0.09$), strong evidence that this has a key influence on memory outcomes. Given that non-multidomain types of CCT were ineffective on memory, and funnel plot analysis of multidomain studies did not show any significant asymmetry (Egger's intercept = 1.75, 95% CI [-1.53, 5.04], $p=0.13$), the subsequent subgroup analyses were performed solely on RCTs of multidomain CCT ($k=14$, N CCT = 680, mean sample size = 48.57, N controls = 655, mean sample size = 46.79).

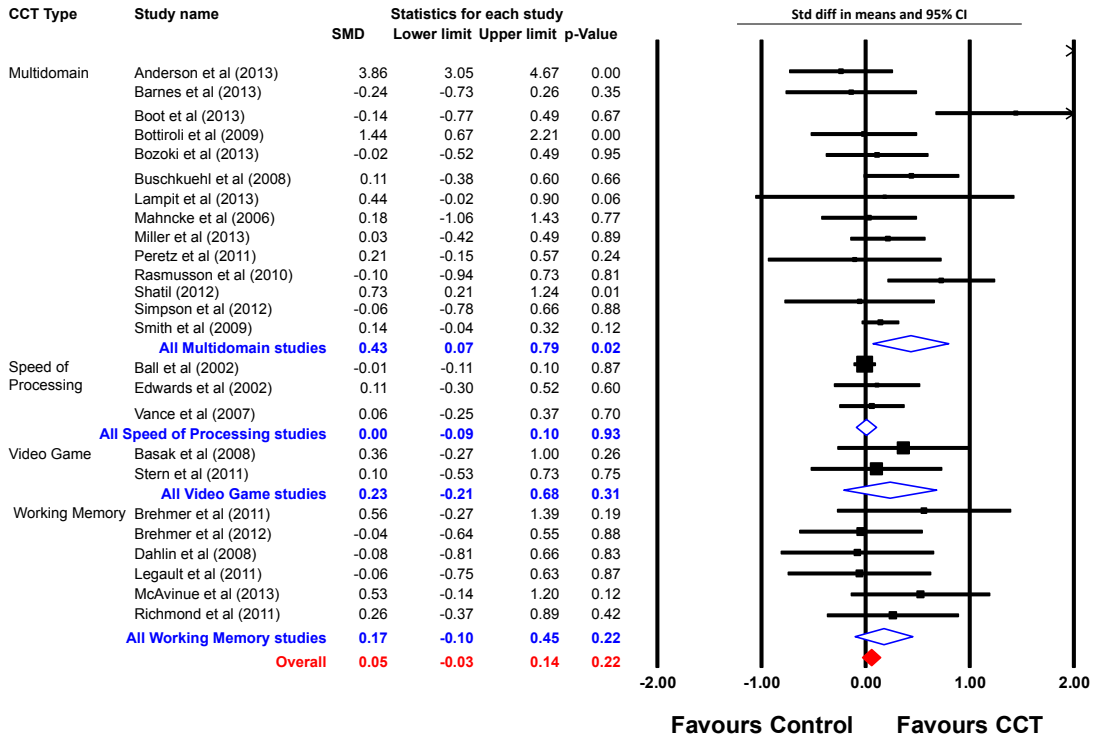


Figure 2.4: Subgroup analysis of memory outcomes by type of CCT

Practice moderators of multidomain CCT efficacy on memory: delivery, dose, session length and frequency. Whilst *centre-based* training produced medium effect size ($k=5$, SMD = 0.50, 95% CI [0.07, 0.93], $p=0.02$, $I^2=63.69\%$, $p=0.02$), *home-based* training was ineffective ($k=9$, SMD = 0.39, 95% CI [-0.11, 0.89], $p=0.13$, $I^2=90.53\%$, $p<0.01$). However, formal test for between-subgroup heterogeneity was non-significant ($Q(1)=0.1$, $p=0.75$).

A total *training dose* of 21-40 hours produced large and significant effect sizes (k=7, SMD = 0.68, 95% CI [0.01, 1.35], p=0.04, I^2=93.03%, p<0.01), whereas smaller doses were ineffective (k=6, SMD = 0.23, 95% CI [-0.11, 0.58], p=0.18, I^2=57.15%, p=0.04), but again between-subgroups heterogeneity test did not reach statistical significance (Q(1)=1.375, p=0.24).

An analysis of *session length* was not attempted due a disproportional distribution of studies with 30-60 minute sessions (k=9) compared to <30 and >60 minute (k=3 and 2, respectively). A subgroup analysis of *session frequency* did not find any moderating effect (>3 sessions/wk: k=7, SMD = 0.54, 95% CI [-0.17, 1.25], p=0.14, I^2=92.64%, p<0.01; 2-3 sessions/wk: k=5, SMD = 0.25, 95% CI [-0.04, 0.54], p=0.09, I^2=49.17%, p=0.09; 1 session/wk: k=2, SMD = 0.68, 95% CI [-0.84, 2.19], p=0.38, I^2=86.06%, p<0.01; between-subgroup (Q(2)=0.804, p=0.69). Similarly, meta-regressions examining memory SMDs against dose, session length and frequency did not yield any significant results (data not reported here).

Study design moderators of multidomain CCT efficacy on memory: control condition, blinding and type of outcomes. Studies that compared CCT to *active control* yielded significant results (k=10, SMD = 0.49, 95% CI [0.04, 0.93], p=0.03, I^2=89.7%, p<0.01), whereas comparison to *no-contact control* groups did not show an effect (k=4, SMD = 0.18, 95% CI [-.36, 0.92], p=0.39, I^2=75.31%, p<0.01), but the difference did not reach statistical significance when tested for between-subgroup heterogeneity (Q(1)=0.27, p=0.61).

The moderating effect of *blinding* was tested after excluding the only two single-blinded studies[44,49], leaving a total number of 12 studies. *Double-blinded* studies showed statistically significant, albeit small effects (k=5, SMD = 0.15, 95% CI [0.01,

0.29], p=0.04, I^2=0.39%, p=0.4), whereas unblinded studies yielded statistically insignificant effects (k=7, SMD = 0.28, 95% CI [-0.1, 0.66], p=0.15, I^2=63.71%, p=0.01). There was no evidence of between-subgroup heterogeneity (Q(1)=0.34, p=0.56).

Memory outcomes based on *computerised tests* were statistically significant (k=7, SMD = 0.37, 95% CI [0.06, 0.67], p=0.02, I^2=61.28%, p=0.02), whereas non-computerised tests did not reach significance (k=9, SMD = 0.38, 95% CI [-0.17, 0.93], p=0.18, I^2=90.55%, p<0.01), yet test for between subgroup heterogeneity was insignificant (Q(1)=0.002, p=0.97).

Study quality moderators of multidomain CCT efficacy on memory. A meta-regression analysis found a small but statistically insignificant inverse relationship between study quality and memory SMDs (b=-0.14, Q(1)=1.45, p=0.22.

2.3.3 Meta-Analysis of Working Memory Outcomes

Training effects. Figure 2.5 shows the k= 23 studies comparing pretest–posttest gains between CCT and control groups on all WM measures (N CCT = 888, mean sample size = 38.61, N controls = 831, mean sample size = 36.13). 18 studies reported more than one WM outcomes, which were combined into one effect size per study using CMD. The combined effect size was small and statistically significant (SMD = 0.26, 95% CI [0.07, 0.46], p=0.01). The heterogeneity between studies was medium- to-large and significant, I^2 = 70.99%, p<0.01. The funnel plot did not show significant asymmetry (Egger's intercept = -0.22, 95% CI [-2.17, 1.73], p=0.41).

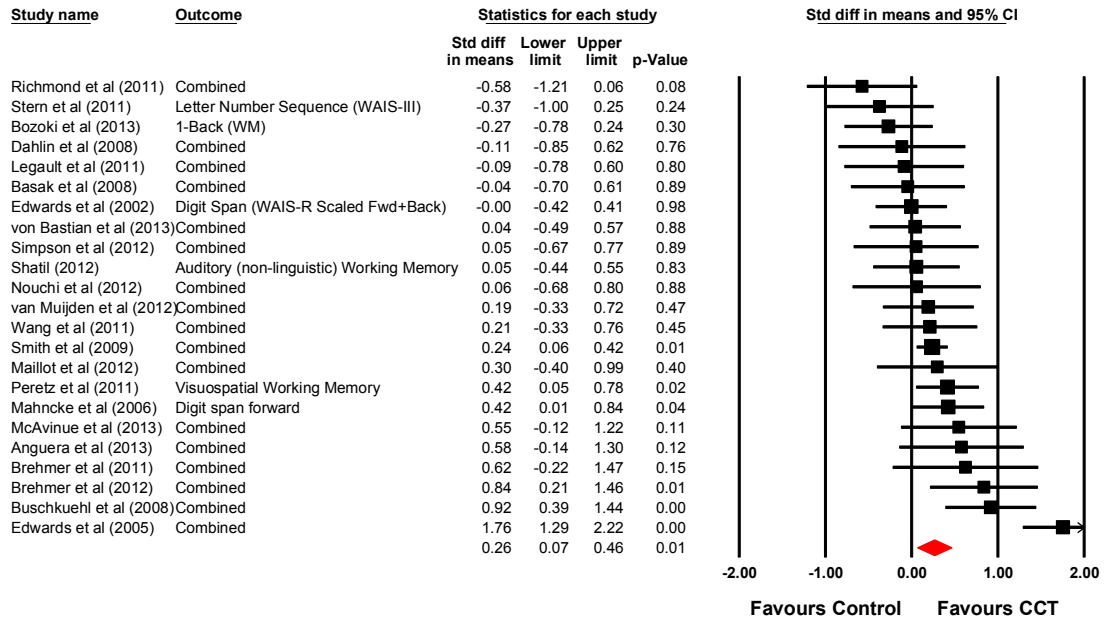


Figure 2.5: Forest plot for effects on working memory (all studies), rank ordered by SMD

Moderating effect of CCT type on working memory outcomes. Only *multidomain* CCT produced statistically significant effects of small size (k=10, SMD = 0.26, 95% CI [0.09, 0.43], p<0.01, I^2=30.05%, p=0.17). Overall, there were no significant effects on working memory outcomes for WM training (k=7, SMD = 0.17, 95% CI [-0.20, 0.54], p=0.37, I^2=54.98%, p=0.04), video game training (k=4, SMD = 0.08, 95% CI [-0.29, 0.44], p=0.68, I^2=0%, p=0.37) or SOP training (k=2, SMD = 0.87, 95% CI [-0.85, 2.60], p=0.32, I^2=96%, p=0<0.01). However, there was no formal evidence of heterogeneity between the five types of CCT (Q(3)=1.39, p=0.71) or between the two most prevalent subtypes (multidomain and WM training): Q(1)=0.19, p=0.66). The remaining subgroup analyses were therefore performed for all CCT studies reporting WM outcomes.

Practice moderators of CCT efficacy on working memory: delivery, dose, session length and frequency. Whilst *home-based* training produced small but statistically significant effect size (k=13, SMD = 0.24, 95% CI [0.06, 0.41], p<0.01,

I^2=36.28%, p=0.09), *centre-based* training was ineffective (k=10, SMD = 0.28, 95% CI [-0.16, 0.72], p=0.21, I^2=83.26%, p<0.01). Formal test for between-subgroup heterogeneity was non-significant (Q(1)=0.03, p=0.87).

A total *training dose* of 20 hours or less was sufficient to produced small-medium effect sizes (k=14, SMD = 0.35, 95% CI [0.02, 0.68], p=0.04, I^2=78.09%, p<0.01), whereas studies that provided a dose of 21-40 hours showed considerably smaller and insignificant effects (k=9, SMD = 0.16, 95% CI [-0.01, 0.33], p=0.06, I^2=17.3%, p=0.29), but again between-groups heterogeneity did not reach statistical significance (Q(1)=1.041, p=0.31).

Studies with *session length* of 30-60 minutes showed significant results (k=14, SMD = 0.31, 95% CI [0.02, 0.59], p=0.03, I^2=78.26%, p<0.01), whereas shorter sessions were ineffective (k=8, SMD = 0.21, 95% CI [-0.07, 0.49], p=0.14, I^2=44.26%, p=0.08; between-subgroup Q(1)=0.244, p=0.62). A subgroup analysis of *session frequency* was performed after removing a single study that used one weekly session[41]. Studies with 2-3 weekly sessions (k=12, SMD = 0.34, 95% CI [-0.01, 0.99], p=0.06, I^2=79.71%, p<0.01) tended to be more effective than 3 or more sessions per week (k=10, SMD = 0.16, 95% CI [-0.05, 0.37], p=0.12, I^2=43.44%, p=0.07), albeit between-subgroup heterogeneity was not evident (Q(1)=0.71, p=0.40). Meta-regressions plotting WM SMDs against dose, session length and frequency did not yield any significant results (data not shown).

Study design moderators of CCT efficacy on working memory: control condition, blinding and type of outcomes. Studies that compared CCT to *active control* yielded significant results (k=18, SMD = 0.34, 95% CI [0.11, 0.57], p<0.01, I^2=73.74%, p<0.01), whereas comparison to *no-contact control* groups did not show

an effect (k=5, SMD = -0.05, 95% CI [-.30, 0.21], p=0.73, I^2=0%, p=0.73). For this moderating factor, significant between- subgroup heterogeneity was found (Q(1)=4.82, p=0.03, see Figure 2.6).

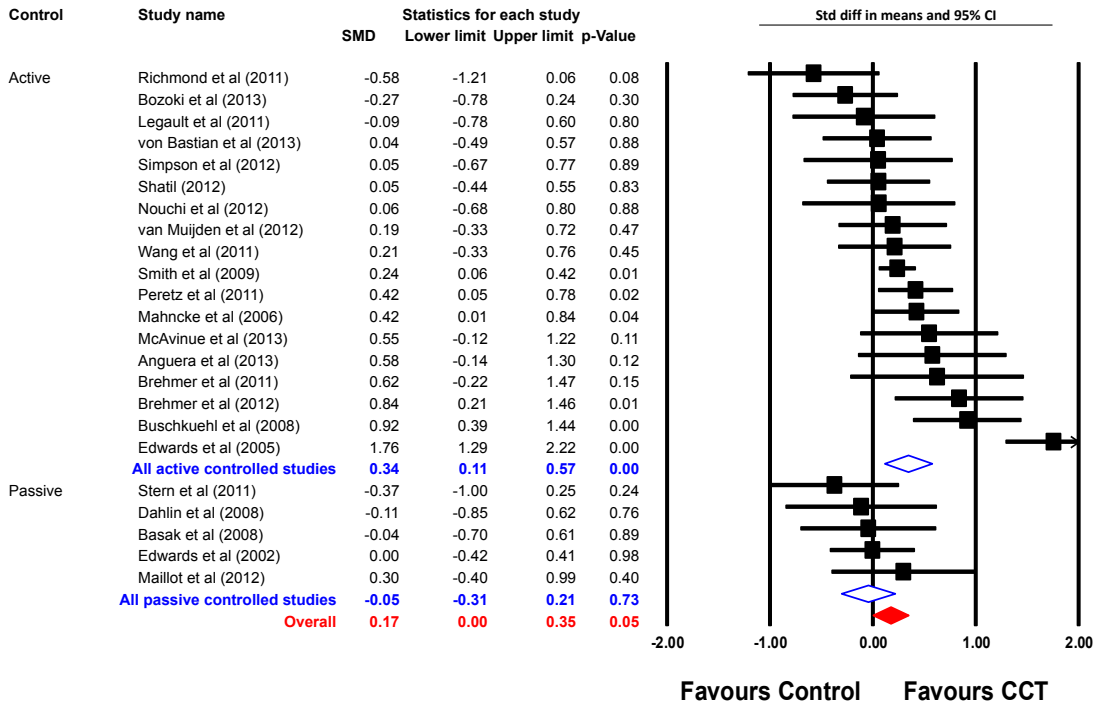


Figure 2.6: Forest plot for effects on working memory by control condition

The moderating effect of *blinding* was tested in only 22 studies, as only one study was assessor-blinded[59]. Only double-blinded studies showed statistically significant results (k=6, SMD = 0.30, 95% CI [0.15, 0.45], p<0.01, I^2=7.41%, p=0.37), whereas insignificant effects were noted for both subject-blind (k=4, SMD = 0.13, 95% CI [-0.19, 0.45], p=0.43, I^2=25.5%, p=0.26) and unblinded studies (k=12, SMD = 0.27, 95% CI [-0.13, 0.68], p=0.19, I^2=82.09%, p<0.01). There was no strong evidence of between-subgroup heterogeneity (Q(2)=0.89, p=0.64).

As opposed to memory outcomes, WM outcomes from *computerised tests* did not reach statistical significance (k=9, SMD = 0.28, 95% CI [-0.06, 0.61], p=0.10,

I^2=70.97%, p<0.01), whereas non-computerised tests did reach significance with a small effect size (k=16, SMD = 0.29, 95% CI [0.02, 0.54], p=0.03, I^2=74.61%, p<0.01), but test for heterogeneity was insignificant as well (Q(1)=0.003, p=0.96).

Study quality moderators of all-type CCT efficacy on working memory. A meta-regression analysis did not find any relationship between study quality and WM outcomes speed SMDs (β =0.04, Q(1)=0.27, p=0.61).

2.3.4 Meta-Analysis of Processing Speed Outcomes

Efficacy. Figure 2.7 shows the k =23 studies comparing pretest–posttest gains between CCT and control groups on all processing speed measures (N CCT = 1,615, mean sample size = 70.22, N controls = 1,456, mean sample size = 63.30). 19 studies reported two or more processing speed outcomes, which were combined into one effect size per study. Two studies[32,45] reported UFOV sub-scores as well as a composite score, and only the latter was included in the analyses. The combined effect size was medium-sized and significant (SMD = 0.40, 95% CI [0.18, 0.63], p<0.01). Heterogeneity between studies was large and significant, I^2 = 83.21%, p<0.01. The funnel plot did not show any significant asymmetry (Egger's intercept = -0.41, 95% CI [-2.16, 1.34], p=0.31).

Moderating effect of CCT types on processing speed outcomes. Statistically significant medium-size effects were noted for studies involving *SOP training* (k=5, SMD = 0.49, 95% CI [0.31, 0.67], p<0.01, I^2=61.56%, p=0.03) and *video games* (k=4, SMD = 0.44, 95% CI [0.07, 0.80], p=0.02, I^2=16.49%, p=0.31). *Multidomain training* did not show statistically significant effects (k=13, SMD = 0.35, 95% CI [-0.16, 0.87], p=0.18, I^2=89.19%, p=0.17), and neither did the single study of WM training (SMD

= 0.37, 95% CI [-0.37, 1.10], p=0.33). No significant between-subgroup heterogeneity was observed (Q(3)=0.35, p=0.95), and hence the remaining of analyses were performed on all studies reporting processing speed outcomes.

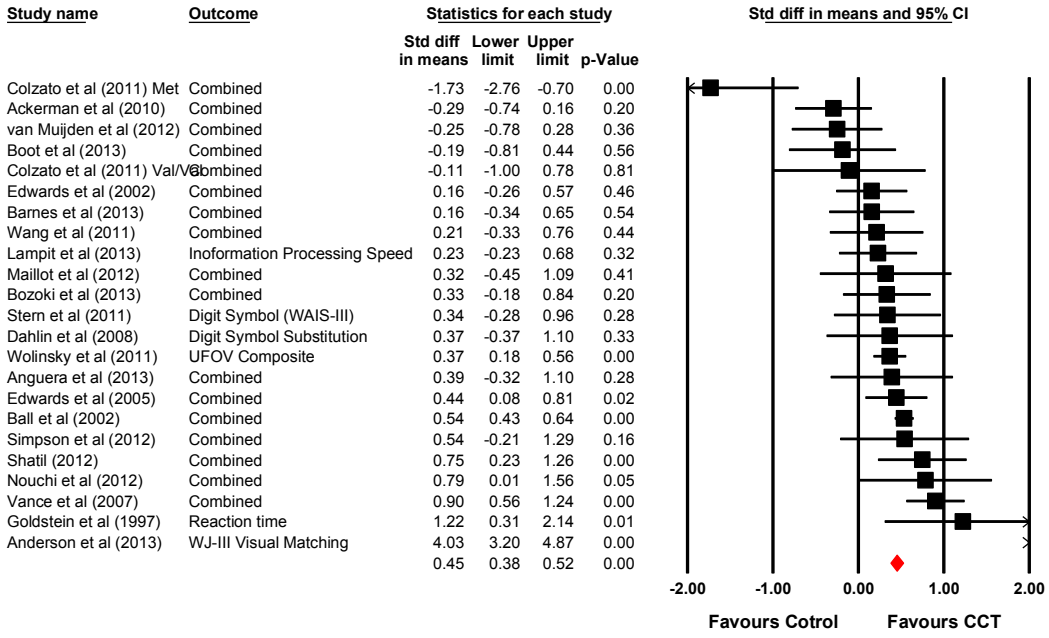


Figure 2.7: Forest plot for effects on processing speed (all studies), rank ordered by SMD

Practice moderators of all-type CCT efficacy on processing speed: delivery, dose, session length and frequency. Only *centre-based* training produced statistically significant effect (k=11, SMD = 0.46, 95% CI [0.34, 0.59], p<0.01, I^2=29.67%, p=0.16). *Home-based* training was ineffective (k=12, SMD = 0.40, 95% CI [-0.20, 1.00], p=0.19, I^2=90.17%, p<0.01), but a formal test for between-subgroup heterogeneity was non-significant (Q(1)=0.04, p=0.85).

A total *training dose* of 20 hours or less produced significant effects (k=11, SMD = 0.41, 95% CI [0.23, 0.58], p<0.01, I^2=57.79%, p<0.01), whereas studies that provided a dose of 21-40 hours showed insignificant results (k=11, SMD = 0.48, 95% CI [-0.13, 1.09], p=0.21, I^2=90.28%, p<0.01), but between-subgroups heterogeneity did

not reach statistical significance ($Q(1)=1.05, p=0.81$). A subgroup analysis of *session length* was not attempted due to a disproportional number of studies with 30-60 minutes per session ($k=15$) compared to less than 30 minutes ($k=5$) and more than 60 minutes ($k=3$).

Studies with 2-3 weekly sessions were effective on processing speed ($k=10$, SMD = 0.48, 95% CI [0.39, 0.57], $p<0.06$, $I^2=0\%$, $p=0.56$), and so were studies with only one session per week ($k=3$, SMD = 0.51, 95% CI [0.12, 0.91], $p=0.01$, $I^2=75.56\%$, $p=0.02$), but more than 3 sessions per week was not effective ($k=10$, SMD = 0.43, 95% CI [-0.32, 1.18], $p=0.26$, $I^2=91.94\%$, $p<0.01$). Between-subgroup heterogeneity was insignificant among the three frequency categories ($Q(2)=0.04, p=0.98$) as well as between 2-3 and >3 weekly sessions ($Q(1)=0.02, p=0.90$). Meta-regressions plotting processing speed SMDs against dose, session length and frequency did not find any significant results (data not reported here).

Study design moderators of all-type CCT efficacy on processing speed: control condition, blinding and type of outcomes. Significant effects were noted for studies comparing CCT to both *active control* ($k=16$, SMD = 0.42, 95% CI [0.08, 0.77], $p=0.01$, $I^2=87.39\%$, $p<0.01$) and *no-contact control* conditions ($k=7$, SMD = 0.37, 95% CI [0.12, 0.62], $p<0.01$, $I^2=43.83\%$, $p=0.1$). A significant between-group heterogeneity was not found ($Q(1)=0.06, p=0.81$). The moderating effect of *blinding* was not tested due to disproportionally large number of unblended studies ($k=13$) compared to studies with subject-blinded ($k=4$), assessor-blinded ($k=4$) and double-blinded ($k=2$) designs.

Effect sizes on processing were similar and statistically significant for both *computerised tests* ($k=17$, SMD = 0.33, 95% CI [0.03, 0.62], $p=0.03$, $I^2=89.43\%$,

p<0.01), and *non-computerised tests* (k=14, SMD = 0.40, 95% CI [0.04, 0.75], p=0.03, I^2=88.66%, p<0.01) with insignificant heterogeneity (Q(1)=0.09, p=0.76).

Study quality moderators of all-type CCT efficacy on processing speed. A meta-regression analysis did not find any relationship between study quality and WM SMDs (b=0.03, Q(1)=0.18, p=0.67).

2.3.5 Meta-Analysis of Attention Outcomes

Efficacy. Figure 2.8 shows the 10 effect sizes comparing pretest–posttest gains between CCT and control groups on all attention measures (N CCT = 367, mean sample size = 36.7, N controls = 302, mean sample size = 30.2). 6 studies reported two or more attention outcomes, which were combined into one effect size per study. The combined effect size was small (SMD = 0.26, 95% CI [0.005, 0.517], p=0.046). The heterogeneity between studies was medium-sized and significant, I^2 = 58.62%, p=0.01. The funnel plot showed a possible albeit not significant asymmetry towards to the left of the funnel (Egger's intercept = 2.23, 95% CI [-1.37, 5.83], p=0.1).

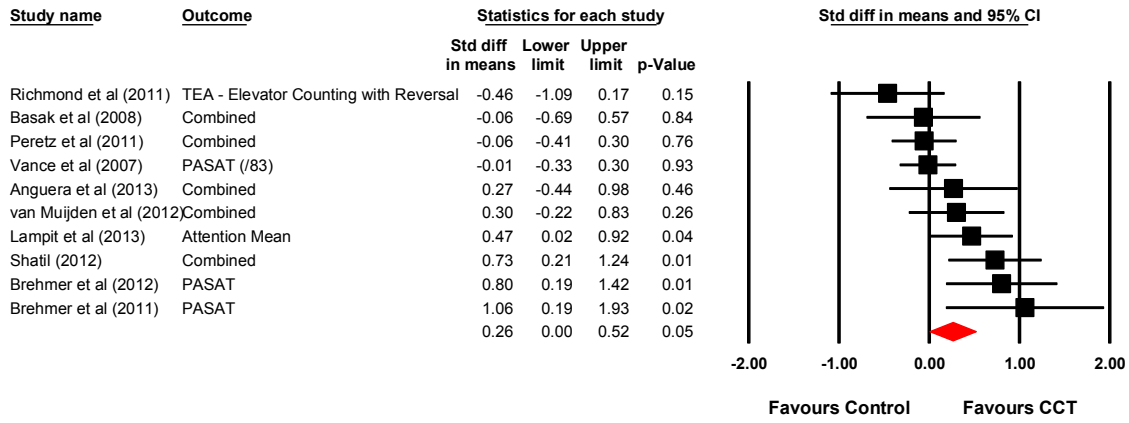


Figure 2.8: Forest plot for effects on attention (all studies), rank ordered by SMD

Moderating effect of CCT types on attention outcomes. Possibly due to the small number of studies reporting attention outcomes, none of the interventions reached the significance threshold, but *multidomain training* showed a small effect with trend towards significance (k=4, SMD = 0.33, 95% CI [-0.02, 0.68], p=0.06, I^2=57.09%, p=0.07). There was no evidence for efficacy for WM training (k=3, SMD = 0.44, 95% CI [-0.5, 1.39], p=0.36, I^2=81.85%, p<0.01) or video games (k=2, SMD = 0.08, 95% CI [-0.39, 0.55], p=0.73, I^2=0%, p=0.49). A single study[69] reported a null effect of SOP training on attention (SMD = -0.01, 95% CI [-0.33, 0.30], p=0.93). No significant between-group heterogeneity was observed (Q(3)=2.57, p=0.46), and thus the following analyses were performed on all studies reporting attention outcomes.

Practice moderators of CCT efficacy on attention: delivery, dose, session length and frequency. Neither *centre-based* training (k=4, SMD = 0.27, 95% CI [-0.1, 0.65], p=0.15, I^2=61.95%, p=0.05) nor *home-based* training (k=6, SMD = 0.26, 95% CI [-0.13, 0.66], p=0.19, I^2=63. 57%, p=0.02) produced significant effects. A total *training dose* of 21-40 hours showed medium effect size (k=4, SMD = 0.40, 95% CI [0.10, 0.69], p<0.01, I^2=22.45%, p=0.28), whereas studies that provided a dose of 20 hours or less showed insignificant results (k=6, SMD = 0.19, 95% CI [-0.17, 0.55], p=0.31, I^2=64.76%, p=0.01), but between-subgroups heterogeneity did not reach statistical significance (Q(1)=0.76, p=0.38).

A subgroup analysis of *session frequency* was performed after removing the single study that used session length of more than 60 minutes[47]. Studies with 30-60 minutes per session showed trend towards significance (k=4, SMD = 0.33, 95% CI [-0.03, 0.69], p=0.07, I^2=57.16%, p=0.07) and studies with session length of 30 minutes or

less were ineffective (k=5, SMD = 0.27, 95% CI [-0.2, 0.74], p=0.25, I^2=70.85%, p<0.01). Between-subgroup heterogeneity was not evident (Q(1)=0.04, p=0.84).

A subgroup analysis of *session length* was performed after removing the single study that used only one weekly session[69]. Non-significant results were noted for both 2-3 weekly sessions (k=5, SMD = 0.26, 95% CI [-0.06, 0.6], p=0.11, I^2=49.9%, p=0.1) and more than 3 sessions per week (k=4, SMD = 0.39, 95% CI [-0.23, 1.01], p=0.214, I^2=72.86%, p=0.01), and between-subgroup heterogeneity was insignificant (Q(1)=0.13, p=0.72) Meta-regressions plotting attention SMDs against dose, session length and frequency did not find any significant results (data not shown).

Study design moderators of all-type CCT efficacy on attention: control condition, blinding and type of outcomes. A subgroup analyses of *control condition* was not performed as only one study[47] used a no-contact control group. None of the *blinding* conditions showed significant results (unblinded k=5, SMD = 0.21, 95% CI [-0.26, 0.67], p=0.38, I^2=71.71%, p<0.01; double-blinded k=3, SMD = 0.36, 95% CI [-0.14, 0.86], p=0.16, I^2=70.72%, p=0.03; subject-blinded k=2, SMD = 0.29, 95% CI [-0.13, 0.71], p=0.18, I^2=0%, p=0.94) and there was no between-subgroup heterogeneity (Q(2)=0.2, p=0.9).

Effect sizes on attention were significant only for *computerised tests*, which also showed low within-subgroup heterogeneity (k=6, SMD = 0.27, 95% CI [0.003, 0.53], p=0.05, I^2=37.43%, p=0.15). Effects on *non-computerised tests* were insignificant (k=4, SMD = 0.29, 95% CI [-0.31, 0.89], p=0.34, I^2=77.26%, p<0.01), but a formal test for between-subgroup heterogeneity was insignificant (Q(1)=0.005, p=0.95).

Study quality moderators of all-type CCT efficacy on attention. A meta-regression analysis did not find any relationship between study quality and attention SMDs (b=0.04, Q(1)=0.33, p=0.56).

2.3.6 Meta-Analysis of Language Outcomes

Efficacy. Figure 2.9 shows the k=7 studies comparing pretest–posttest gains between CCT and control groups on all language measures (N CCT = 218, mean sample size = 31.14, N controls = 214, mean sample size = 30.57). Four studies reported two or more language outcomes, which were combined into one effect size per study. The combined effect size was medium (SMD = 0.47, 95% CI [0.02, 0.92], p=0.04). The heterogeneity between studies was large and significant, I^2 = 81.0%, p<0.01. The funnel plot did not show evidence of asymmetry (Egger's intercept = -0.94, 95% CI [-17.00, 15.10], p=0.44).

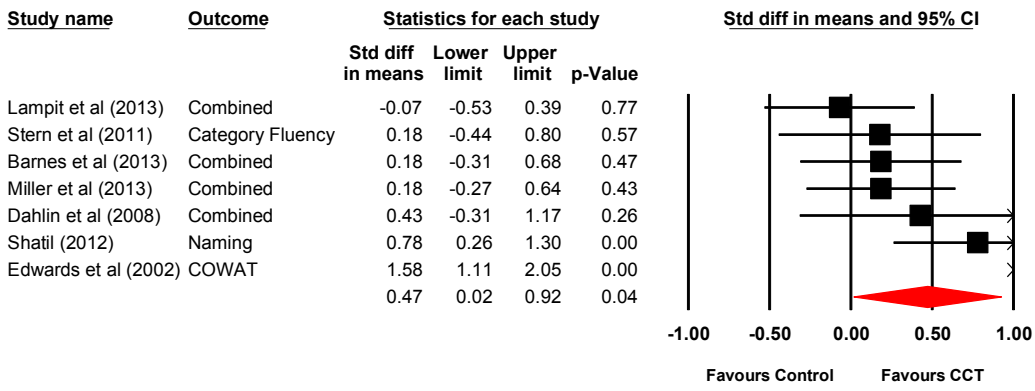


Figure 2.9: Forest plot for effects on language (all studies), rank ordered by SMD

Moderating effect of CCT types on language outcomes. A subgroup analysis of CCT types was not possible as four of the seven studies used multidomain programs and there were only single reports for SOP training[54], video games[67] and WM

training[53]. The rest of the subgroup analyses were therefore attempted using all studies reporting language outcomes.

Practice moderators of all-type CCT efficacy on language: delivery, dose, session length and frequency. A subgroup analysis of delivery was not performed due to a disproportionally large of *centre-based* CCT studies (k=5) compared to studies of *home-based* CCT (k=2). A subgroup analysis of *training dose* did not find any significant effects for either 20 hours or less (k=3, SMD = 0.74, 95% CI [-0.21, 1.69], p=0.12, I^2=89.16%, p<0.01) or 20-40 hours (k=4, SMD = 0.26, 95% CI [-0.10, 0.63], p=0.16, I^2=50.0%, p=0.11). A subgroup analysis of *session duration* was not performed as only one study[61] used 20-25 minutes per sessions, whereas all the other studies had a session length of 30-60 minutes. Similarly, the same study[61] was the only one to include more than three weekly sessions, and since all the other studies used a *session frequency* of 2-3 sessions per week, a subgroup analysis could not be performed. A series meta-regressions examining language SMDs against dose, session length and frequency did not find any significant results (data not shown).

Study design moderators of all-type CCT efficacy on language: control condition, blinding and type of outcomes. No significant effects were noted from either *active-controlled* (k=3, SMD = 0.29, 95% CI [-0.20, 0.78], p=0.25, I^2=66.29%, p=0.05) or *no-contact control* studies (k=4, SMD = 0.60, 95% CI [-0.14, 1.35], p=0.11, I^2=86.03%, p<0.01).

A subgroup analysis of *blinding condition* found a significant between-subgroup heterogeneity (Q(1)=3.13, p=0.08, see Figure 2.10) between unblinded designs (k=5, SMD = 0.65, 95% CI [0.08, 1.21], p=0.03, I^2=81.48%, p<0.01) and double-blinded studies (k=2, SMD = 0.18, 95% CI [-0.31, 0.68], p=0.47, I^2=0%, p=0.46). A subgroup

analysis of *computerised testing* was not performed as only one study[65] used a computerised language test.

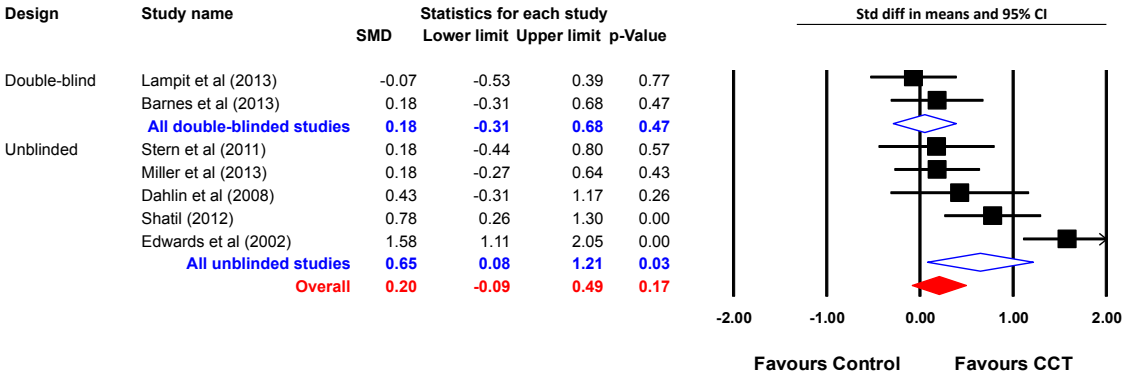


Figure 2.10: Forest plot for CCT effects on language by blinding condition

Study quality moderators of all-type CCT efficacy on language. A meta-regression analysis found a significant inverse relationship between language SMDs and PEDro scores (b=-0.24, $Q(1)$=5.76, p=0.02, see Figure 2.11).

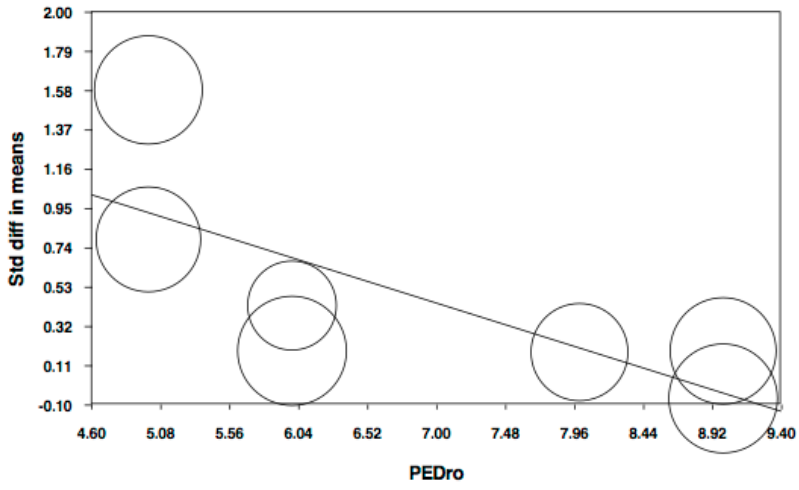


Figure 2.11: Meta-regression of PEDro scores on language SMDs. Note: circle diameters are proportional to sample size

2.3.7 Meta-Analysis of Visuospatial Outcomes

Efficacy. Figure 2.12 shows the $k = 8$ studies comparing pretest–posttest gains between CCT and control groups on all visuospatial measures (N CCT = 267, mean sample size = 33.37, N controls = 260, mean sample size = 32.5). Four studies reported two or more visuospatial outcomes, which were combined into one effect size per study. The combined effect size was small and significant (SMD = 0.31, 95% CI [0.07, 0.54], p=0.01). The heterogeneity between studies was statistically insignificant, $I^2 = 40.29\%$, p=0.11. The funnel plot showed a trend towards asymmetry towards the right of the mean (Egger's intercept = 2.54, 95% CI [-0.82, 5.89], p=0.06).

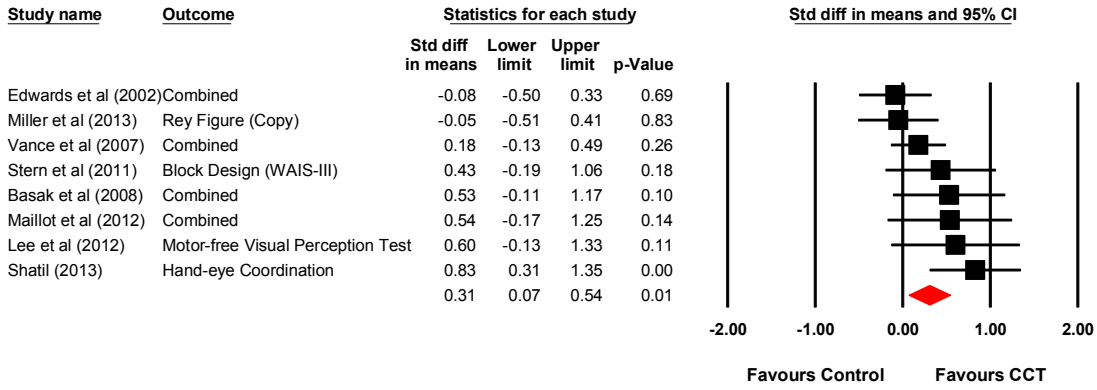


Figure 2.12: Forest plot for effects on visuospatial performance (all studies), rank ordered by SMD

Moderating effect of CCT types on visuospatial outcomes. Only results from the two video game training studies [47,71] were statistically significant (SMD = 0.48, 95% CI [0.03, 0.93], p=0.03, I^2=0%, p=0.83). Insignificant results were found from multidomain CCT (k=3, SMD = 0.42, 95% CI [-0.15, 0.99], p=0.15, I^2=69.04%, p=0.04) and SOP training (k=3, SMD = 0.14, 95% CI [-0.15, 0.44], p=0.33, I^2=26.89%, p=0.25). Between-subgroup heterogeneity was not found (Q(2)=1.80,

p=0.40), and the rest of the moderator analyses were attempted using all studies reporting visuospatial outcomes.

Practice moderators of CCT efficacy on visuospatial measures: delivery, dose, session length and frequency. A subgroup analysis of delivery was not performed as only one study[61] used *home-based* CCT. A subgroup analysis of *training dose* found significant between-group heterogeneity ($Q(1)=7.14$, $p<0.01$, see Figure 2.13), whereby a large effect size was found for total dose of 21-40 hours (k=4, SMD = 0.61, 95% CI [0.31, 0.92], $p<0.01$, $I^2=0\%$, $p=0.78$) and insignificant effects for smaller doses (k=4, SMD = 0.10, 95% CI [-0.12, 0.32], $p=0.39$, $I^2=7.53\%$, $p=0.36$). Furthermore, meta- regression found a significant positive relationship between training dose and visuospatial SMDs ($b=0.02$, $Q(1)=5.83$, $p=0.02$, see Figure 2.14)

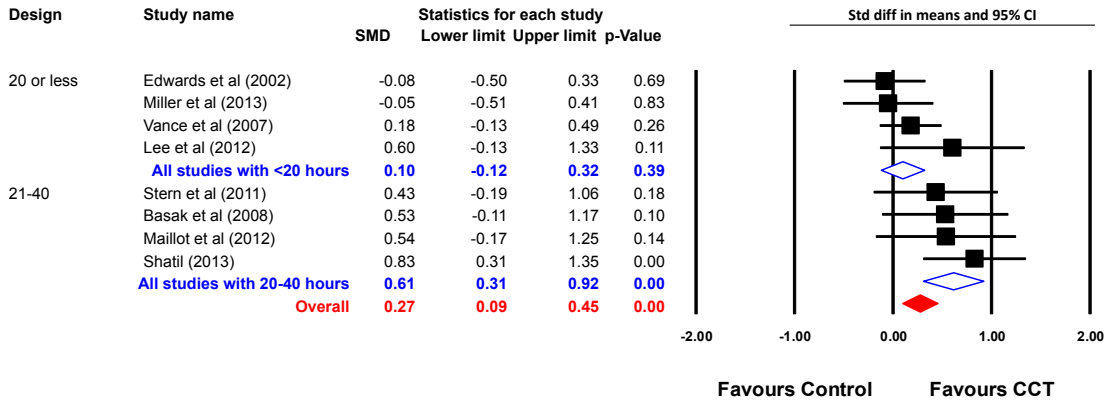


Figure 2.13: Forest plot for CCT effects on visuospatial measures by training dose

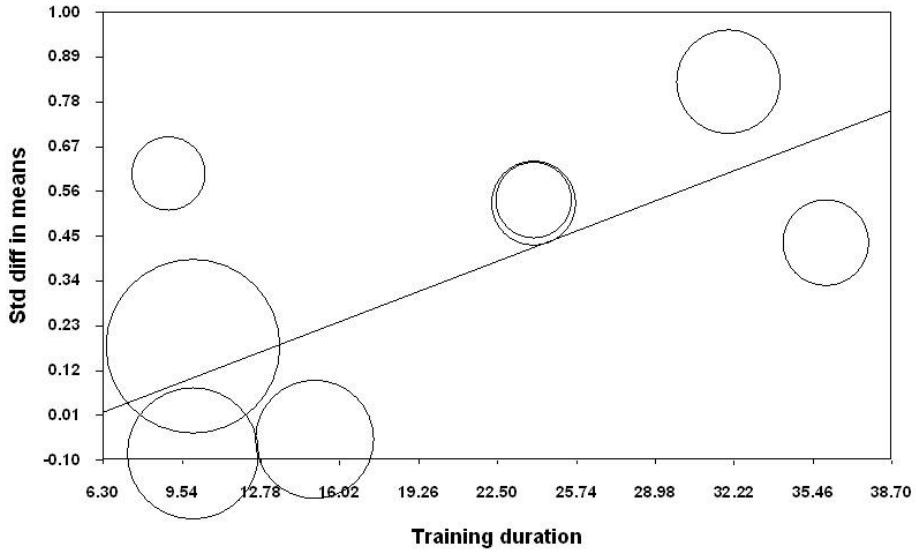


Figure 2.14: Meta-regression of CCT dose (total training hours) on visuospatial SMDs.

Only a *session duration* of 30-60 minutes was effective on visuospatial measures (k=5, SMD = 0.33, 95% CI [0.01, 0.64], p=0.04, I^2=52.44%, p=0.08). Shorter sessions were ineffective (k=2, SMD = 0.21, 95% CI [-0.42, 0.84], p=0.51, I^2=55.57%, p=0.14), but there was no between-subgroup heterogeneity (Q(1)=0.10, p=0.75). Moderator analysis of *session frequency* was not performed as there was only one study with more than 3 weekly sessions[61] and only one study with a single session per week[69]. A series of meta-regressions did not find any significant relationship between visuospatial SMDs and session duration or frequency (data not reported).

Study design moderators of CCT efficacy on visuospatial measures: control condition, blinding and type of outcomes. Results from *active-controlled* trials were positive (k=3, SMD = 0.48, 95% CI [0.04, 0.93], p=0.03, I^2=58.45%, p=0.09), whereas *no-contact control* studies did not show significant effect (k=5, SMD = 0.18, 95% CI [-0.1, 0.46], p=0.20, I^2=24.13%, p=0.26), but no between-subgroup heterogeneity was noted (Q(1)=1.25, p=0.26).

Figure 2.15 presents a subgroup analysis of *computerised testing*. There was a significant between-group heterogeneity ($Q(1)=4.98$, $p=0.03$) between significant outcomes for computerised testing ($k=4$, SMD = 0.48, 95% CI [0.20, 0.75], $p<0.01$, $I^2=17.41\%$, $p=0.30$) versus null results for paper-based visuospatial measures ($k=5$, SMD = 0.09, 95% CI [-0.10, 0.29], $p=0.35$, $I^2=0\%$, $p=0.44$). A subgroup analysis of *blinding condition* was not performed as all studies were unblinded.

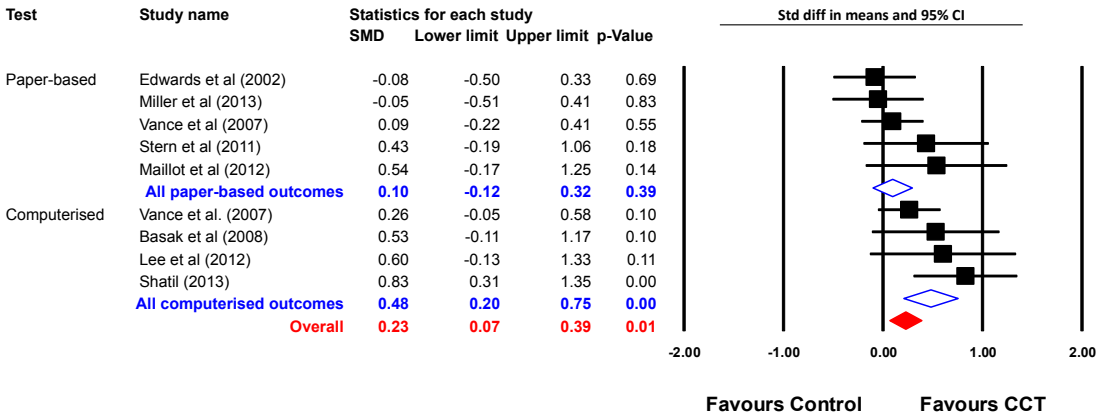


Figure 2.15: Forest plot for CCT effects on language by test administration

Study quality moderators of all-type CCT efficacy on visuospatial measures. A meta-regression analysis did not find any relationship between visuospatial SMDs and PEDro scores ($b<0.01$, $Q(1)<0.01$, $p=0.99$).

2.3.8 Meta-Analysis of Executive Function Outcomes

Efficacy. Figure 2.16 shows the $k = 24$ studies comparing pretest–posttest gains between CCT and control groups on the broad domain of executive functions (N CCT = 1,415, mean sample size = 58.36, N controls = 1,345, mean sample size = 56.04). 19 studies reported two or more executive functions outcomes, which were combined into one effect size per study. The combined effect size was statistically insignificant (SMD = -0.01, 95% CI [-0.09, 0.06], $p=0.72$). Furthermore, heterogeneity between

studies was null, $I^2 = 0\%$, p=0.66. The funnel plot did not reveal asymmetry (Egger's intercept = 0.17, 95% CI [-0.49, 0.83], p=0.30).

A *post—hoc* analyses of executive functions subdomains showed a trend towards significance in the unfavourable direction for the Trail Making Test A and B outcomes, with small, negative and homogenous effect (k=9, SMD = -0.20, 95% CI [-0.41, 0.005], p=0.06, I^2=32.82%, p=0.16). None of the outcomes for other executive subdomains (inhibition, planning, reasoning, shifting and task-switching) neared statistical significance, and no further subgroup analyses were conducted.

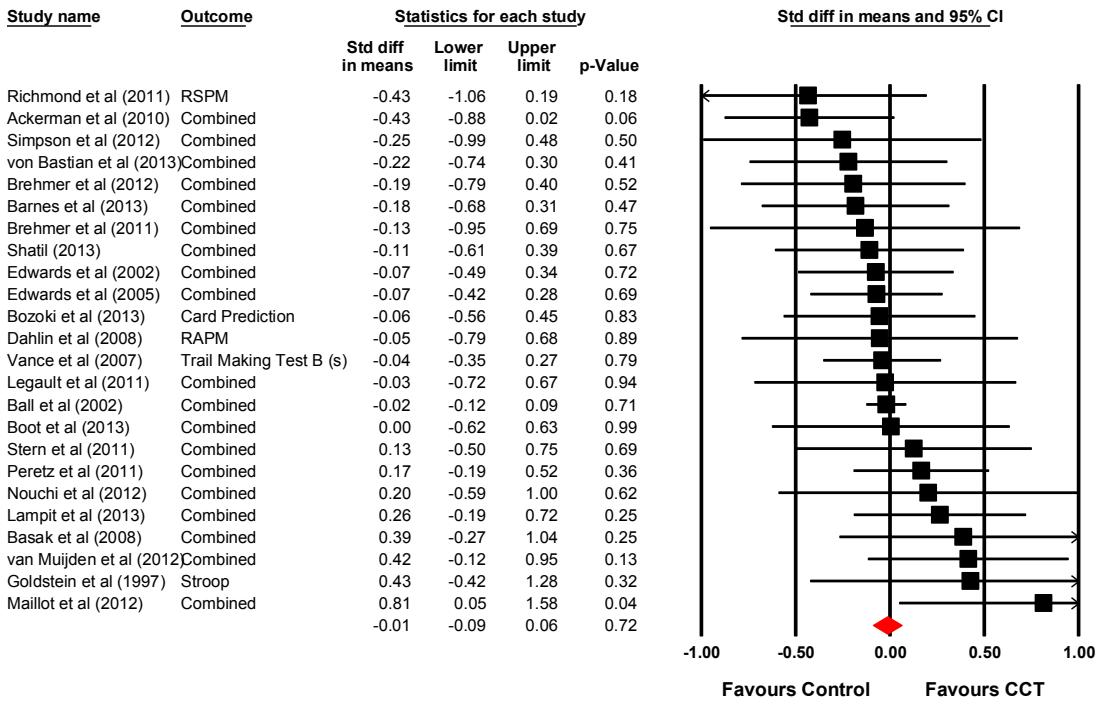


Figure 2.16: Forest plot for effects on executive functions (all studies), rank ordered by SMD

2.4 Discussion

2.4.1 Summary

Table 2.3 summarises these results, charting visually the evidence for CCT efficacy and moderators of efficacy across the seven cognitive domains.

		All outcomes	*Memory*	*Working memory*	*Processing speed*	*Attention*	*Language*	*Visuospatial*	*Executive*
	All studies	0.27**	0.28**	0.26**	0.41**	0.26*	0.47*	0.31*	-0.01
CCT type	Multidomain	0.28*	0.43*	0.26**	0.35	0.33	0.26	0.42	0.05
	SOP	0.27**	0.004	0.87	0.48**	-0.01		0.14	-0.03
	Video games	0.30*	0.23	0.08	0.44*	0.08	0.18	0.48*	0.29
	WM	0.26	0.17	0.17	0.37	0.44			-0.19
Delivery	Centre-based	0.30**	0.22*	0.28	0.46**	0.27	0.59	0.37**	0
	Home-based	0.23	0.36	0.24**	0.4	0.27	0.19	-0.05	-0.06
Dose	<20 hours	0.23**	0.1	0.35*	0.40**	0.19	0.74	0.10	-0.05
	21-40 hours	0.34*	0.57*	0.16	0.48	0.40**	0.26	0.61**	0.16
Session Length	<30 min	0.11	0.14	0.21	-0.11	0.27	0.18	0.21	-0.001
	31-60 min	0.33**	0.34*	0.31	0.50**	0.33	0.52	0.38*	-0.04
Frequency	1/wk	0.39*	0.44	0.21	0.51*	-0.01		0.18	-0.04
	2-3/wk	0.16**	0.15	0.34	0.47**	0.26	0.52	0.43*	0.0008
	>3/wk	0.22	0.44	0.17	0.43	0.39	0.18	-0.05	-0.10
Control	Active	0.28*	0.37*	0.34**	0.42*	0.29*	0.29	0.48*	-0.05
	No-contact	0.21*	0.13	-0.05	0.37**	-0.06	0.6	0.18	0.01
Design	Double-blind	0.24**	0.14	0.29**	0.35**	0.36	0.05		0.03
	Assessor-blind	0.86	0.99	0.25	2.26				-0.02
	Subject-blind	0.19	-0.02	0.13	0.15	0.29			0.17
	Unblinded	0.22*	0.23*	0.27	0.25	0.21	0.64*	0.31*	-0.05
Tests	Computerised	0.32**	0.37**	0.25	0.33*	.0.27*		0.48**	0.07
	Paper	0.24**	0.21	0.29*	0.40*	0.29	0.42	0.09	-0.06

Table 2.3: Overview of efficacy and moderators of efficacy for CCT in older adults. Coloured cells indicate significant outcomes from a meta-analysis: Yellow = SMD 0-0.4; Orange = SMD 0.4-0.6; Red = SMD ≥0.6. White depicts non-significant results with SMDs and grey shows where insufficient studies were available for analysis. * $p < 0.05$. ** $p < 0.01$. Red borders mark moderators of ineffectiveness.

To date this is the most comprehensive systematic review of the CCT in the field of healthy aging. Maximally, it combines data from 37 trials and 4310 subjects. For the first time, the objective of this meta-analysis was not simply a description of aggregate efficacy but also an understanding of what moderators may be impacting on efficacy variance.

Taken together, this review suggests CCT is effective: significant low-to-moderate effect sizes were observed for memory, WM, processing speed, attention and visuospatial outcomes when specifically compared to active control conditions. Efficacy on language was weak and mainly present in studies of low quality. Notably, no efficacy on executive function was observed in any analysis.

Some alternative explanations for the observed effect sizes can be ruled out. Publication bias was uncommon and thus an unlikely explanation for efficacy. Also, 70% of the studies were active-controlled and so this is not a major limitation in the literature. However, it is possible that at least some of the active-controlled study did not adequately control for expectation bias[42], given only 8 of the 26 active-controlled studies (31%) were double-blinded, introducing possible bias. Overall, study quality was moderate (average PEDro score = 6.49), and so further work to improve the quality of evidence is required.

For the first time, this meta-analysis found evidence for efficacy moderators, revealing several CCT factors that meet the stringent Q-test criteria for between-subgroup heterogeneity, along with other "trend" moderating factors that distinguish between effective and non-effective training (but did not meet Q-test threshold).

Significant moderating effects were found for type of CCT on memory favouring multidomain training; control type in WM favouring active-controlled studies; blinding and study quality of language outcomes favouring unblinded studies and a negative relationship between study quality and results; and total training dose on visuospatial skills favouring a total dose of 21-40 hours. Other possible moderators that did not meet the Q-test threshold are given in **Table 2.2**, but should be considered as practice factors when designing future studies rather than as definite evidence of moderating effect[33]. Each of these potential moderating factors are next discussed in more detail.

2.4.2 The Anatomy of CCT

Along with interventions aimed at reducing cardiovascular risk factors, cognitive interventions including CCT have been frequently studied as possible primary and secondary ARCD prevention strategies. These studies require large sample sizes and take years to complete, but lack of knowledge about how to optimisize the interventions or measure outcomes reduce their feasibility. For example, two large trials involving CT (along with other interventions) are currently underway[72,73], each involving a sample size of 1,200 participants for a period of five years. Despite both being members of a major European collaboration, these two trials use markedly different cognitive interventions. The Multidomain Alzheimer Preventive Trial (MAPT[73]) provides 12 120-minute strategy training sessions, starting with 8 sessions of reasoning training and followed by 4 sessions of mnemonic training. Conversely, the training protocol of the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER[72]) begins with 10 group 60-90 minute sessions, after which participants train on a WM CCT program for 10-15 minutes three times

per week for six months at home. As discussed below it is clear that these design choices are not supported by the findings of this review.

Since the effects of CCT tend to be limited to the trained domains[45], *multidomain programs* are more likely to tap the cognitive complexity of everyday tasks and global measures of cognition. Indeed, as can be seen in **Table 2**, only multidomain training was found effective on memory (SMD=0.43) and WM (SMD=0.26). It should be emphasised that of the 20 studies reporting outcomes from multidomain CCT, 19 trained all targeted domains throughout the whole training period, and only one[46] trained a set of domains for half of the time and a different set for the remaining period, reporting negative outcomes. Furthermore, this review found *WM training* as particularly ineffective on transfer tasks, consistent with a recent meta-analysis of WM in younger cohorts[74]. Similarly, neither *SOP training* nor *video games* were effective beyond the trained domains. A balanced *multidomain program* is therefore key moderator of CCT effectiveness when aiming for positive memory outcomes.

Supervised administration might also prove another important component in the effectiveness of CCT, as centre-based, therapist-guided CCT programs were effective on memory (SMD=0.22), processing speed (SMD=0.46) and visuospatial skills (SMD=0.37), whereas home-based training was effective only on WM (SMD=0.24). Trainers may help ensure adherence, increase motivation, support trainees' work on challenging tasks and provide nonspecific effects such as social interaction and activities, involving organising travel to the training centre times, considered important elements in cognitive remediation therapy[75]. Furthermore, as the training program progresses, tasks may become more challenging and technical problem may arise, bringing about frustration on behalf of trainees that could be largely prevented

when guidance and support are available. For example, in their active-controlled trial of *home-based* CCT, Smith et al[25] reported 19 dropouts due to frustration, of which 16 dropped out from the CCT group. Indeed, group administration of non-computerised memory training was found as more effective than individual training in several trials[76-78] and in a meta-analysis of mnemonic training in older adults[79], whereas several trials of different reasoning strategy training did not find difference between the two training conditions[80,81]. Conversely, whilst the only trial to date comparing centre-based to home-based administration did not find differences between the two forms of administration[32], it should be noted that the trial included only ten hours of training on one exercise, and the outcome measure was very similar to the trained task (SOP training). Determining the added value of centre-based training is therefore a critical point for further research, as this type of administration is likely to be more expensive than training at-home[8], and may therefore only be justified from a health economic view if supervised administration produces a major difference in CCT outcomes.

Finally, **Table 2.3** suggests two important findings concerning the temporal dynamics of CCT. First, short sessions (<30 minutes) are probably not challenging enough to induce cognitive benefits. Along with home-based administration, this finding may partially explain the negative results of Owen et al's[82] large trial of CCT in young and middle-aged adults (besides several other design flaws with this study[83]). It is possible that short sessions are insufficient to induce synaptic plasticity, more likely to occur after 30-60 minute of stimulation[84]. Second, here it was found that training programs that consist of more than 3 sessions per week are clearly ineffective. This is in line with prior work suggesting that 4-7 sessions per week is considerably less effective than more dispersed training schedules[85,86]. It is possible that there is a maximal

threshold intensity for cognitive training (possibly three hours per week), after which factors such as exhaustion may interfere with training gains.

2.4.3 Recommendations for Future CCT Trials

As opposed to all other domains, this review did not find any effect of CCT on executive functions. In fact, significant results on executive functions were found for only one trial, which provided 24 1-hour sessions of a centre-based multidomain program using Nintendo Wii exergames versus wait-list control[22]. As physical exercise has clear effects on executive functions[87], it is possible that CCT programs could incorporate cognitively challenging exergames to tap this otherwise unresponsive cognitive domain. However, because exergames involve costly equipment and may not be well suited to the physical capabilities of many older adults, new training exercises will need to be developed and trialled. On the other hand, it should be also noted that complementing CCT with physical exercise did not increase the effect on executive function in two of the trials included in this review[46,65], and so much further work in this area is required.

Language skills are another domain for further research and development. This review found only six studies that reported language outcomes, and whilst the overall result of the meta analysis is positive (SMD=0.47, p=0.04, see **Figure 2.9**), significant results were obtained only when studies were unblinded (see **Figure 2.10**), and poor study quality correlated with language outcomes (see **Figure 2.11**). More high quality studies are required to establish that CCT programs can enhance language skills in the elderly.

Most trials included in this review, especially those conducted in the past 10 years, compared the efficacy of CCT to an active control condition. The results of the meta analysis show that CCT effects were greater in active-controlled trials than in trials with wait-list or otherwise passive control groups. Active control conditions are vital in order to control for a range of nonspecific factors[9] and expectancy bias[42], and must be included in future clinical trials, particularly in light of the fact that that major clinical trials such as ACTIVE[45], MAPT[73] and FINGER[72] did not include active control arms and hence their outcomes are difficult to interpret.

2.4.4 Limitations of the Current Meta-analysis

Despite limiting its scope to studies involving tightly-defined CCT and randomised control designs, this review is based on a heterogeneous set of studies with different intervention design and hundreds of outcome measures. As a result, many of the observed effects were accompanied by significant between-study heterogeneity, which in turn makes it more challenging to reveal between-subgroup variability in moderator analyses. Also, study outcomes were weighted according to variance regardless of the quality of evidence, which may have brought about, in some cases, an overestimation of effects (especially for the language domain). Thus, findings from this review should be regarded as a guide on the likely conditions for CCT efficacy and inefficacy, rather than a final judgement on a particular training strategy or program.

This review was also designed to focus on immediate training gains on neuropsychological measures. It therefore provides no indication about the durability of the observed gains, nor the transfer from the latter into real-life outcomes such as everyday memory, mobility, daily function or risk of long term cognitive morbidity.

Similarly, it did not discriminate between possible psychometric differences between outcome measures within a specific domain, such as internal and external validity, reliability and their neuropsychological rationale. Indeed, the CMA software combines test outcomes from a similar domain blindly, irrespective of the relative neuropsychological merits of the outcomes. This limitation therefore requires a critical interpretation of the findings, as well as to more specific analyses of the data.

2.4.5 Conclusions

In healthy older adults, CCT can produce gains in memory, WM, processing speed, attention and visuospatial skills. There is no substantive evidence for efficacy on language or executive functions. Further research may be required to develop and validate CCT exercises that can tap these two domains. Reducing some of the methodological heterogeneity between studies by adopting some new standardised CCT design features will help mature the field. Use of centre-based multidomain programs, standard active control designs, keeping session frequency to less than three times per week and more than 30 minutes per session are suggested based on the moderator effects found here.

References

1. Thies W, Bleiler L, Alzheimer's Association. 2013 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2013;9(2):208–245. doi:10.1016/j.jalz.2013.02.003.

2. Marioni RE, Valenzuela MJ, van den Hout A, Brayne C, Matthews FE, MRC Cognitive Function and Ageing Study. Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS ONE*. 2012;7(12):e50940. doi:10.1371/journal.pone.0050940.

3. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508–2516. doi:10.1056/NEJMoa022252.

4. Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA*. 2002;287(6):742–748.

5. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*. 2011;(1):CD006220. doi:10.1002/14651858.CD006220.pub2.

6. Hindin SB, Zelinski EM. Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. *J Am Geriatr Soc*. 2012;60(1):136–141. doi:10.1111/j.1532-5415.2011.03761.x.

7. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up. *Am J Geriatr Psychiatry*. 2009;17(3):179–187. doi:10.1097/JGP.0b013e3181953b57.

8. Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: a systematic review. *PLoS ONE*. 2012;7(7):e40588. doi:10.1371/journal.pone.0040588.

9. Gates N, Valenzuela M. Cognitive exercise and its role in cognitive function in older adults. *Curr Psychiatry Rep*. 2010;12(1):20–27. doi:10.1007/s11920-009-0085-y.

10. Jak AJ, Seelye AM, Jurick SM. Crosswords to computers: a critical review of popular approaches to cognitive enhancement. *Neuropsychol Rev*. 2013;23(1):13–26. doi:10.1007/s11065-013-9226-5.

11. Buschert V, Bokde ALW, Hampel H. Cognitive intervention in Alzheimer disease. *Nat Rev Neurol*. 2010;6(9):508–517. doi:10.1038/nrneurol.2010.113.

12. Gates NJ, Sachdev PS, Fiatarone Singh MA, Valenzuela M. Cognitive and

memory training in adults at risk of dementia: a systematic review. *BMC Geriatr*. 2011;11:55. doi:10.1186/1471-2318-11-55.

13. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. *Ageing Res Rev*. 2013;12(1):263–275. doi:10.1016/j.arr.2012.07.003.

14. Papp KV, Walsh SJ, Snyder PJ. Immediate and delayed effects of cognitive interventions in healthy elderly: a review of current literature and future directions. *Alzheimers Dement*. 2009;5(1):50–60. doi:10.1016/j.jalz.2008.10.008.

15. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry*. 2011;168(5):472–485. doi:10.1176/appi.ajp.2010.10060855.

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. In: Vol 6. 2009:e1000100. doi:10.1371/journal.pmed.1000100.

17. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev*. 2003;(4):CD003260. doi:10.1002/14651858.CD003260.

18. Gates NJ, Valenzuela M, Sachdev PS, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: a randomised double blind, sham controlled, longitudinal trial. *BMC Geriatr*. 2011;11:19. doi:10.1186/1471-2318-11-19.

19. Anguera JA, Boccanfuso J, Rintoul JL, et al. Video game training enhances cognitive control in older adults. *Nature*. 2013;501(7465):97–101. doi:Letter.

20. Strauss EH, Sherman EMS, Spreen O. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. 3rd ed. Oxford: Oxford University Press; 2006.

21. Bornstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-analysis (version 2).

22. Maillot P, Perrot A, Hartley A. Effects of interactive physical-activity video-game training on physical and cognitive function in older adults. *Psychol Aging*. 2012;27(3):589–600. doi:10.1037/a0026268.

23. Nouchi R, Taki Y, Takeuchi H, et al. Brain training game improves executive functions and processing speed in the elderly: a randomized controlled trial. *PLoS ONE*. 2012;7(1):e29676. doi:10.1371/journal.pone.0029676.

24. Mahncke HW, Connor BB, Appelman J, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: a randomized, controlled study. *Proc Natl Acad Sci USA*. 2006;103(33):12523–12528.

doi:10.1073/pnas.0605194103.

25. Smith GE, Housen P, Yaffe K, et al. A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study. *J Am Geriatr Soc*. 2009;57(4):594–603. doi:10.1111/j.1532-5415.2008.02167.x.

26. Rosen AC, Sugiura L, Kramer JH, Whitfield-Gabrieli S, Gabrieli JD. Cognitive training changes hippocampal function in mild cognitive impairment: a pilot study. *J Alzheimers Dis*. 2011;26 Suppl 3:349–357. doi:10.3233/JAD-2011-0009.

27. Gajewski PD, Falkenstein M. Training-induced improvement of response selection and error detection in aging assessed by task switching: effects of cognitive, physical, and relaxation training. *Front Hum Neurosci*. 2012;6:130. doi:10.3389/fnhum.2012.00130.

28. Schmiedek F, Lövdén M, Lindenberger U. Hundred Days of Cognitive Training Enhance Broad Cognitive Abilities in Adulthood: Findings from the COGITO Study. *Front Aging Neurosci*. 2010;2. doi:10.3389/fnagi.2010.00027.

29. Optale G, Urgesi C, Busato V, et al. Controlling memory impairment in elderly adults using virtual reality memory training: a randomized controlled pilot study. *Neurorehabil Neural Repair*. 2010;24(4):348–357. doi:10.1177/1545968309353328.

30. Wild-Wall N, Falkenstein M, Gajewski PD. Neural Correlates of Changes in a Visual Search Task due to Cognitive Training in Seniors. *Neural Plasticity*. 2012;2012:11. doi:10.1155/2012/529057.

31. Theill N, Schumacher V, Adelsberger R, Martin M, Jäncke L. Effects of simultaneously performed cognitive and physical training in older adults. *BMC Neurosci*. 2013;14(1):103. doi:10.1186/1471-2202-14-103.

32. Wolinsky FD, Vander Weg MW, Howren MB, et al. Interim analyses from a randomised controlled trial to improve visual processing speed in older adults: the Iowa Healthy and Active Minds Study. *BMJ Open*. 2011;1(2):e000225. doi:10.1136/bmjopen-2011-000225.

33. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2011.

34. Colzato LS, van Muijden J, Band GPH, Hommel B. Genetic Modulation of Training and Transfer in Older Adults: BDNF ValMet Polymorphism is Associated with Wider Useful Field of View. *Front Psychol*. 2011;2:199. doi:10.3389/fpsyg.2011.00199.

35. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. *Phys Ther*. 2003;83(8):713–721.

36. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency

in meta-analyses. *BMJ*. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557.

37. Engels EA, Schmid CH, Terrin N, Olkin I, Lau J. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med*. 2000;19(13):1707–1728.

38. Boot WR, Champion M, Blakely DP, Wright T, Souders DJ, Charness N. Video games as a means to reduce age-related cognitive decline: attitudes, compliance, and effectiveness. *Front Psychol*. 2013;4:31. doi:10.3389/fpsyg.2013.00031.

39. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.

40. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–634.

41. Wang M-Y, Chang C-Y, Su S-Y. What's Cooking? - Cognitive Training of Executive Function in the Elderly. *Front Psychol*. 2011;2:228. doi:10.3389/fpsyg.2011.00228.

42. Boot WR, Simons DJ, Stothart C, Stutts C. The Pervasive Problem With Placebos in Psychology: Why Active Control Groups Are Not Sufficient to Rule Out Placebo Effects. *Perspect Psychol Sci*. 2013;8(4):445–454.

43. Ackerman PL, Kanfer R, Calderwood C. Use it or lose it? Wii brain exercise practice and reading for domain knowledge. *Psychol Aging*. 2010;25(4):753–766. doi:10.1037/a0019277.

44. Anderson S, White-Schwoch T, Parbery-Clark A, Kraus N. Reversal of age-related neural timing delays with training. *Proc Natl Acad Sci USA*. 2013;110(11):4357–4362. doi:10.1073/pnas.1213555110.

45. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271–2281.

46. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) Trial: A Randomized Controlled Trial to Enhance Cognitive Function in Older Adults. *JAMA Intern Med*. 2013;173(9):797–804. doi:10.1001/jamainternmed.2013.189.

47. Basak C, Boot WR, Voss MW, Kramer AF. Can training in a real-time strategy video game attenuate cognitive decline in older adults? *Psychol Aging*. 2008;23(4):765–777. doi:10.1037/a0013494.

48. Bottiroli S, Cavallini E. Can computer familiarity regulate the benefits of computer-based memory training in normal aging? A study with an Italian sample of older adults. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2009;16(4):401–418. doi:10.1080/13825580802691763.

49. Bozoki A, Radovanovic M, Winn B, Heeter C, Anthony JC. Effects of a computer-based cognitive exercise program on age-related cognitive decline. *Arch Gerontol Geriatr*. 2013;57(1):1–7. doi:10.1016/j.archger.2013.02.009.

50. Brehmer Y, Rieckmann A, Bellander M, Westerberg H, Fischer H, Bäckman L. Neural correlates of training-related working-memory gains in old age. *Neuroimage*. 2011;58(4):1110–1120. doi:10.1016/j.neuroimage.2011.06.079.

51. Brehmer Y, Westerberg H, Bäckman L. Working-memory training in younger and older adults: training gains, transfer, and maintenance. *Front Hum Neurosci*. 2012;6:63. doi:10.3389/fnhum.2012.00063.

52. Buschkuehl M, Jaeggi SM, Hutchison S, et al. Impact of working memory training on memory performance in old-old adults. *Psychol Aging*. 2008;23(4):743–753. doi:10.1037/a0014342.

53. Dahlin E, Nyberg L, Bäckman L, Neely AS. Plasticity of executive functioning in young and older adults: immediate training gains, transfer, and long-term maintenance. *Psychol Aging*. 2008;23(4):720–730. doi:10.1037/a0014296.

54. Edwards JD, Wadley VG, Myers RES, Roenker DL, Cissell GM, Ball KK. Transfer of a speed of processing intervention to near and far cognitive functions. *Gerontology*. 2002;48(5):329–340.

55. Edwards JD, Wadley VG, Vance DE, Wood K, Roenker DL, Ball KK. The impact of speed of processing training on cognitive and everyday performance. *Aging Ment Health*. 2005;9(3):262–271. doi:10.1080/13607860412331336788.

56. Goldstein J, Cajko L, Oosterbroek M, Michielsen M, Van Houten O, Salverda F. VIDEO GAMES AND THE ELDERLY. *soc behav pers*. 1997;25(4):345–352. doi:10.2224/sbp.1997.25.4.345.

57. Lampit A, Hallock H, Moss R, et al. A Dose-Response Relationship between Computerized Cognitive Training and Global Cognition in Older Adults (under review).

58. Lee Y, Lee C-R, Hwang B. Effects of Computer-aided Cognitive Rehabilitation Training and Balance Exercise on Cognitive and Visual Perception Ability of the Elderly TI . *Journal of Physical Therapy Science*. 2012;24(9):885–887.

59. Legault C, Jennings JM, Katula JA, et al. Designing clinical trials for assessing the effects of cognitive training and physical activity interventions on cognitive outcomes: the Seniors Health and Activity Research Program Pilot (SHARP-P) study, a randomized controlled trial. *BMC Geriatr*. 2011;11:27. doi:10.1186/1471-2318-11-27.

60. McAvinue LP, Golemme M, Castorina M, et al. An evaluation of a working memory training scheme in older adults. *Front Aging Neurosci*. 2013;5:20. doi:10.3389/fnagi.2013.00020.

61. Miller KJ, Dye RV, Kim J, et al. Effect of a computerized brain exercise

program on cognitive performance in older adults. *Am J Geriatr Psychiatry*. 2013;21(7):655–663. doi:10.1016/j.jagp.2013.01.077.

62. Peretz C, Korczyn AD, Shatil E, Aharonson V, Birnboim S, Giladi N. Computer-based, personalized cognitive training versus classical computer games: a randomized double-blind prospective trial of cognitive stimulation. *Neuroepidemiology*. 2011;36(2):91–99. doi:10.1159/000323950.

63. Rasmusson DX, Rebok GW, Bylsma FW, Brandt J. Effects of Three Types of Memory Training in Normal Elderly. *Aging, Neuropsychology, and Cognition*. 1999;6(1):56–66. doi:doi: 10.1076/anec.6.1.56.790.

64. Richmond LL, Morrison AB, Chein JM, Olson IR. Working memory training and transfer in older adults. *Psychol Aging*. 2011;26(4):813–822. doi:10.1037/a0023631.

65. Shatil E. Does combined cognitive training and physical activity training enhance cognitive abilities more than either alone? A four-condition randomized controlled trial among healthy older adults. *Front Aging Neurosci*. 2013;5:8. doi:10.3389/fnagi.2013.00008.

66. Simpson T, Camfield D, Pipingas A, Macpherson H, Stough C. Improved Processing Speed: Online Computer-based Cognitive Training in Older Adults. *Educational Gerontology*. 2013;38(7):445–458. doi:doi: 10.1080/03601277.2011.559858.

67. Stern Y, Blumen HM, Rich LW, Richards A, Herzberg G, Gopher D. Space Fortress game training and executive control in older adults: a pilot intervention. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn*. 2011;18(6):653–677. doi:10.1080/13825585.2011.613450.

68. van Muijden J, Band GPH, Hommel B. Online games training aging brains: limited transfer to cognitive control functions. *Front Hum Neurosci*. 2012;6:221. doi:10.3389/fnhum.2012.00221.

69. Vance D, Dawson J, Wadley V, et al. The accelerate study: The longitudinal effect of speed of processing training on cognitive performance of older adults. *Rehabilitation Psychology*. 2007;52(1):89–96. doi:doi:10.1037/0090-5550.52.1.89.

70. Bastian von CC, Langer N, Jäncke L, Oberauer K. Effects of working memory training in young and old adults. *Mem Cognit*. 2013;41(4):611–624. doi:10.3758/s13421-012-0280-7.

71. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006–1012. doi:10.1016/S1474-4422(12)70191-6.

72. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimers Dement*. 2013. doi:10.1016/j.jalz.2012.09.012.

73. Gillette-Guyonnet S, Andrieu S, Dantoine T, et al. Commentary on “A

roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. *Alzheimers Dement*. 2009;5(2):114–121. doi:10.1016/j.jalz.2009.01.008.

74. Melby-Lervåg M, Hulme C. Is working memory training effective? A meta-analytic review. *Dev Psychol*. 2013;49(2):270–291. doi:10.1037/a0028228.

75. Wykes T, Spaulding WD. Thinking about the future cognitive remediation therapy--what works and could we do better? *Schizophr Bull*. 2011;37 Suppl 2:S80–90. doi:10.1093/schbul/sbr064.

76. Valentijn SAM, van Hooren SAH, Bosma H, et al. The effect of two types of memory training on subjective and objective memory performance in healthy individuals aged 55 years and older: a randomized controlled trial. *Patient Educ Couns*. 2005;57(1):106–114. doi:10.1016/j.pec.2004.05.002.

77. Flynn TM, Storandt M. Supplemental group discussions in memory training for older adults. *Psychol Aging*. 1990;5(2):178–181.

78. Hastings EC, West RL. The relative success of a self-help and a group-based memory training program for older adults. *Psychol Aging*. 2009;24(3):586–594. doi:10.1037/a0016951.

79. Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychol Aging*. 1992;7(2):242–251.

80. Baltes PB, Sowarka D, Kliegl R. Cognitive training research on fluid intelligence in old age: what can older adults achieve by themselves? *Psychol Aging*. 1989;4(2):217–221.

81. Calero MD, García-Berbén TM. A self-training program in inductive reasoning for low-education elderly: tutor-guided training vs. self-training. *Arch Gerontol Geriatr*. 1997;24(3):249–259.

82. Owen AM, Hampshire A, Grahn JA, et al. Putting brain training to the test. *Nature*. 2010;465(7299):775–778. doi:10.1038/nature09042.

83. Zelinski EM. Scientific critique of BBC/ Nature Brain Training Experiment. *SharpBrains*. 2010. Available at: http://sharpbrains.com/blog/2010/05/10/scientific-critique-of-bbc-nature-brain-training-experiment/. Accessed November 3, 2013.

84. Lüscher C, Nicoll RA, Malenka RC, Muller D. Synaptic plasticity and dynamic modulation of the postsynaptic membrane. *Nat Neurosci*. 2000;3(6):545–550. doi:10.1038/75714.

85. Ballard K, Sternberg DA, Hardy JL, Scanlon M, M. Training-related improvements in cognitive performance persist over time but depend on age; an online study including > 140,000 participants. In: New Orleans; 2012.

86. Penner I-K, Vogt A, Stöcklin M, Gschwind L, Opwis K, Calabrese P. Computerised working memory training in healthy adults: a comparison of two different training schedules. *Neuropsychol Rehabil*. 2012;22(5):716–733. doi:10.1080/09602011.2012.686883.

87. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci*. 2008;9(1):58–65. doi:10.1038/nrn2298.

Chapter 3: A Dose-Response Relationship between Computerised Cognitive Training and Global Cognition in Older Adults

3.1 Introduction

Maintaining cognitive performance in late life is an important priority as nations try to meet the challenges posed by population aging[1]. Advanced age is typically accompanied by a decline in global cognition (GC)[2-4], however, individual trajectories exhibit great variability[5,6] and there is rising interest in non-pharmacological cognitive-based interventions to arrest and even reverse these trends[7-11]. GC summarizes performance across multiple cognitive domains such as memory, processing speed, language, executive function and attention by averaging scores in each domain into a single composite score[12,13]. Among older individuals, GC composites are predictors of key outcomes such as everyday functioning[14,15], job performance[16], mobility[17,18], falls[19], and incidence of dementia[12]. Indeed, dementia is itself defined, "by progressive acquired global impairments of cognitive skills and ability to function independently"[20]. For these reasons, composite scores of GC have been advanced as an endpoint for prevention-orientated randomized controlled trials (RCTs) in elderly at-risk for dementia[21-24].

Computer-assisted cognitive training (CCT) is a prescriptive and efficient way of delivering cognitively challenging exercises using game-like stimuli for the purpose of cognitive enhancement[25,26]. Whilst not uniformly effective[27-29], reviews of CCT trials in the elderly report positive domain-specific cognitive outcomes[7,9,25] (see **Chapter 2**), in line with literature linking a more active cognitive lifestyle with reduced dementia risk[30-33] and compression of cognitive morbidity[34]. But clinical implementation of CCT in this age group is limited by three major knowledge gaps[8,9]. First, there is no high quality evidence supporting the efficacy of any CCT regimen on *far-transfer* outcomes such as GC, general

everyday functioning, or dementia incidence in those without cognitive impairment[10,11,23,27,35] (see **Chapter 2**). In this respect, design of the CCT program is likely to be influential. Unidomain training does not tend to transfer beyond tasks that share similar cognitive demands as the training itself[36-38]. In fact **Chapter 2** showed that multidomain training may be more appropriate when targeting general cognitive performance. Second, as identified in **Chapter 2**, inadequate double-blinding is another methodological issue for cognitive interventions that are particularly susceptible to Hawthorne effects[39]. Third, and perhaps most importantly, dose-response relationships between CCT and GC are yet to be established, nor a detailed understanding of the decay rate for any putative therapeutic effects, essential information for clinical implementation[9] and technological innovation.

The objective of the Timecourse Trial was to examine the net effect of CCT on GC and its four component cognitive domains in older adults with a range of dementia risk factors, as well as chart the evolution of clinical benefits during and 12-months after the cessation of training. We hypothesised that: 1)CCT will induce improvement in GC over and above active control training; 2)Training effects will increase gradually over the training period and wane gradually after training cessation; and 3)Training effects will be still significant three months after training cessation. To test these hypotheses, we randomly assigned 80 older adults to 36 sessions of either supervised, centre-based, multi-domain CCT or fully matched active control memory and attention-based training.

3.2 Methods

Inclusion and exclusion criteria. Inclusion criteria were 65 years of age or older, English fluency, ability to attend 3 sessions per week at the training centre and sufficient physical ability to use a computer. Exclusion criteria were a history, diagnosis or treatment for dementia, diagnosis or treatment for depression in last 6 months, stroke in last 12 months,

major neurological and/or psychiatric disorder requiring current treatment, lack of personal informant, already undertaking a CCT program or current alcohol abuse. Further exclusion criteria included Mini Mental State Examination (MMSE) ≤23, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) > 3.3, or Geriatric Depression Scale (15-item GDS) ≥8. This study was approved by the Human Research Ethics Committee at the University of New South Wales, Sydney. All participants provided written informed consent prior to randomization. All procedures took place in a training centre in Sydney, Australia.

Dementia risk factors. For each participant we computed a dementia risk factor sum (DRFS) based on a single point for any of the following: age ≥ 85 years, education ≤10years, any cardiovascular risk factor (current or past smoker, hypercholesterolemia, hypertension, ischemic heart disease, atrial fibrillation or diabetes), physical inactivity by CHAMPS estimated caloric all cause activity <1843[40], family history of dementia, subjective memory complaint based on GPCOG questions[41], or baseline memory domain score below 1.5SD of age-matched norms. The maximum theoretical DRFS is therefore 12. **Figure 3.1A** shows the frequency for each possible DFRS score. **Fig 3.1B** shows the frequency for individual risk factors within the whole sample. The average DFRS in our sample was 3.3 (±SEM 0.19), ranging from 1 – 9. All subjects therefore carried at least one recognized dementia risk factor and 47% had 3-4 risk factors.

Randomization and blinding. Participants were randomized using a computer-generated randomization in a 1:1 ratio. Assessors were blinded to group allocation and participants were not aware of the study hypotheses. Allocation was concealed until the first day of training and on-going participant blinding achieved by describing CCT as a "diversified set of cognitive exercises", and AC as "comprehension and memory exercises." Both interventions were administered in a supervised group format of one trainer to ten

participants (maximum) during three 30-45 minute sessions per week for a total of 36 sessions over 12-weeks, in a designated training room. A member of the study team supervised all training sessions.

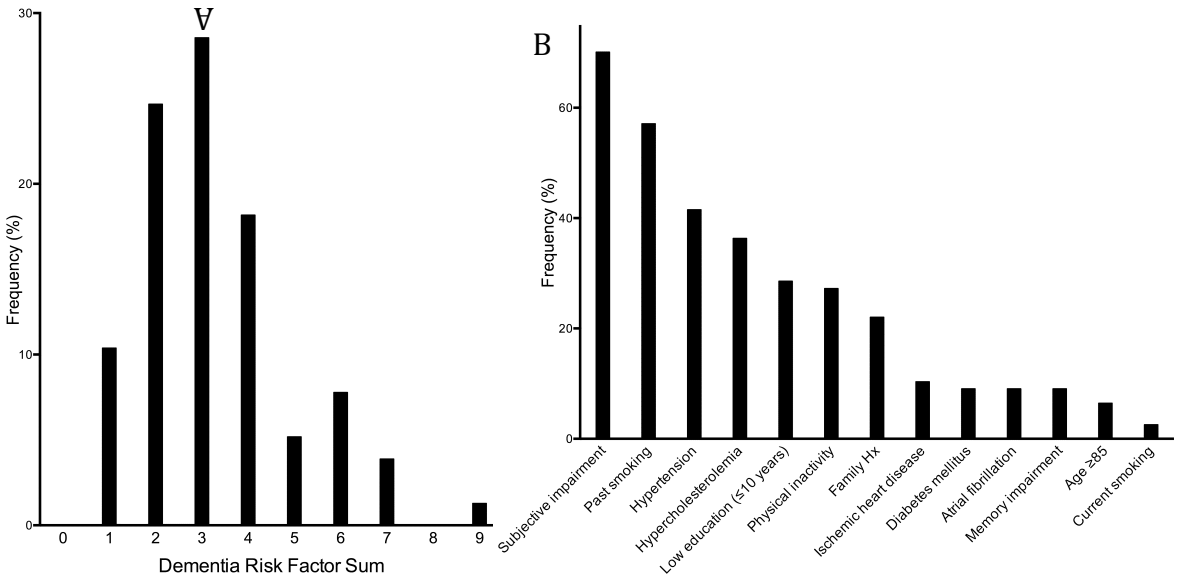


Figure 3.1: Frequency of cumulative (A) and specific (B) dementia risk factors across the whole ITT sample (N = 77).

Computerized Cognitive Training (CCT). We designed and administered a CCT program based on 24 exercises from the COGPACK package, Version 8.1 (Marker Software) to cover the five cognitive domains: memory, attention, response speed, executive functions and language. Each exercise contained 4-8 levels of increasing difficulty. The exercises were administered according to a predefined order that ensured equal (≈20%) allocation of training time on each cognitive domain. The complete COGPACK training regimen is described in the **Appendix 1**. A brief description of each exercise is provided in **Appendix 2**.

Active Control (AC). This intervention was developed for a previous RCT to control for general sensory-motor stimulation, computer use, socialization, motivation, simple learning

and memory demands, and other non-specific effects inherent to supervised CCT[42]. Participants viewed seven National Geographic videos per session on computer and answered multiple-choice questions immediately after each presentation. An electronic library of the 390 videos and associated multiple choice questions are available from the corresponding author.

Outcome measures. The primary outcome was change across four cognitive domain composites (memory, information processing speed, executive functions and global cognition) over six timepoints: baseline and after 9 and 36 training sessions (FU1 and 2, respectively), as well as 3, 12 and 52 weeks after training cessation (FU3, 4 and 5 respectively).

Memory and information processing speed z-score composites were obtained from the *Mindstreams* battery[43]. Executive function z-score composite was defined as the average of Mindstreams Stroop Interference test and CANTAB Stockings of Cambridge problems solved in minimum moves score. Global Cognition Score was obtained by averaging these three z-domain scores. *Mindstreams* tests have three alternate forms that provide good test-retest reliability, are sensitive to differences between healthy elderly and those with mild cognitive impairment, and have been used widely in RCTs[44]. The CANTAB Stockings of Cambridge test is a validated measure of planning and spatial problem solving[45].

In addition, at three of the five FU assessments we evaluated the language domain by averaging performance in the Controlled Oral Word Association Test (COWAT)[46], and short forms of the Boston Naming Test[47] (baseline and FUs 2, 4 and 5). In-house computerized versions of the Recognition Memory Test[48] and WAIS-IV Matrix Reasoning were also administered at these timepoints (baseline and FUs 2, 4 and 5). These four tests were included in the more expansive *post hoc* Global Cognitive Score. Finally, to assess potential

effects of CCT on everyday performance, we administered the Bayer Activities of Daily Living Scale[49] at baseline and follow-up 5.

Statistical analysis. In order to assess the efficacy of CCT over the six timepoints, we conducted linear mixed-modeling repeated-measures (MMRM) analyses using SPSS version 21 (IBM Statistics). Our model included main effects for Group and Time and a Group X Time interaction term. Each cognitive domain score was tested separately. MMRM incorporates a model for missing data values and so avoids discrete imputation or omission of cases[50]. All analyses are therefore intention-to-treat (ITT).

Within-group effect sizes (Cohen's *d*) were calculated by subtracting mean baseline scores from mean score at each time point divided by standard deviation at baseline. Bias-corrected net effect size (NES) were estimated by subtracting Cohen's *d* of the AC group from that of the CCT group, and then applying a bias correction factor $1-(3\div4[(n_{CCT}-n_{AC}-2)-1])$[51]. Absolute differences between CCT and AC for outcomes at each follow-up time point were also calculated along with the associated 95% confidence interval.

3.3 Results

Participants, Attrition & Protocol Adherence

A total of 80 older participants were enrolled into this prospectively registered RCT (ACTRN12611000702910). Of these, 77 participants (39 in the CCT group and 38 in the AC group) completed baseline assessment and are included in all intention-to-treat (ITT) analyses. Twelve participants (15.6%) withdrew during the intervention period (8 in the CCT group, 4 in the AC group, 2-sided χ^2 $p = .347$), and 10 additional participants (13%, five in each group) were lost to longitudinal follow-up (see **Figure 3.2**). No baseline sociodemographic or clinical differences were noted between dropouts and those who

completed intervention**.** There were also no systematic differences in protocol adherence in the CCT group (35.1 sessions, 97.5%) compared to AC training (34.7 sessions, 96.4%, p-value = 0.581).

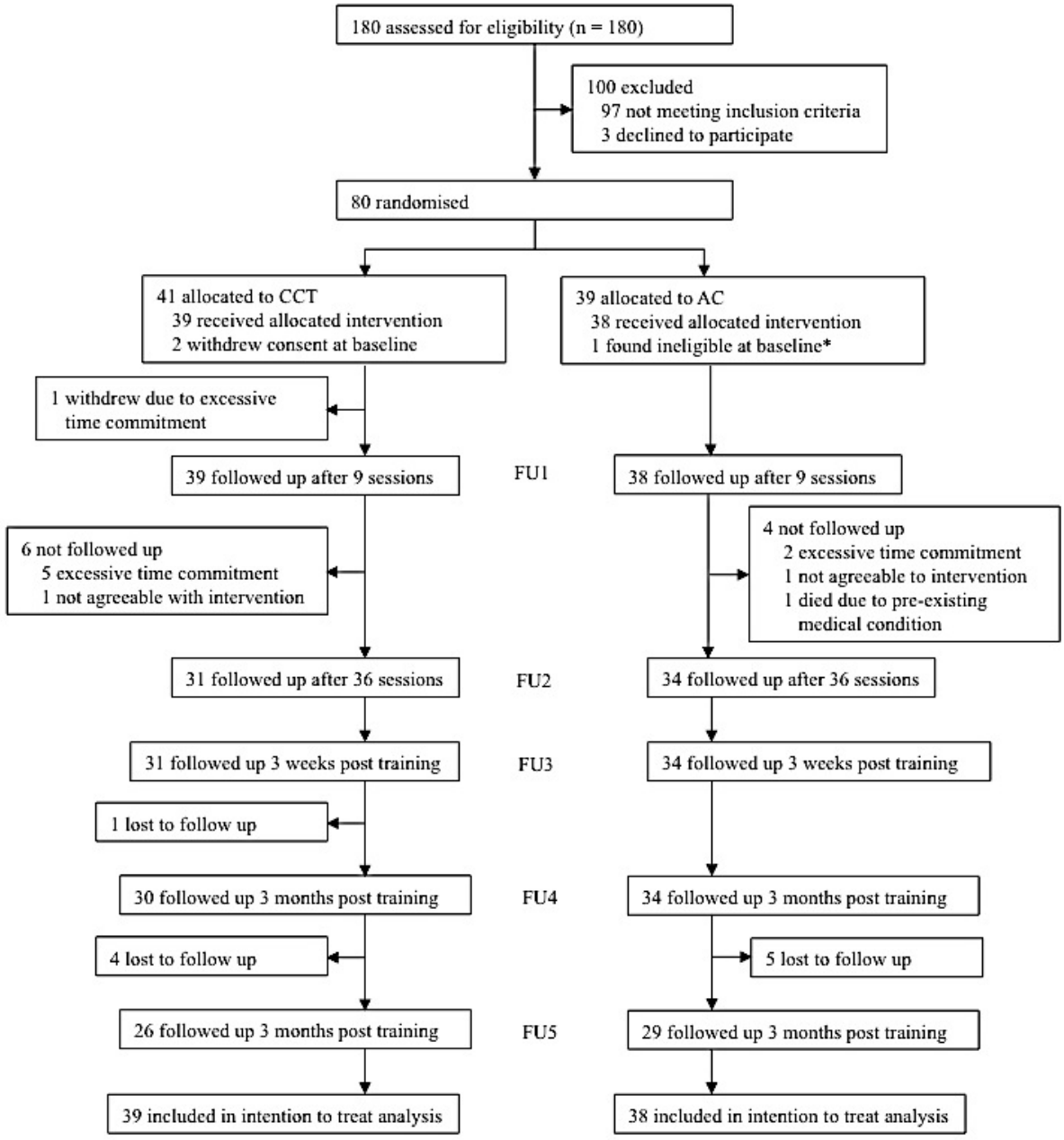


Figure 3.1: Study design and participant flow

At baseline, the age range of participants was 65 to 90 years (mean age 72.1, SD = 6.2), 68.8% were female, MMSE scores ranged from 24 to 30 (mean MMSE 28, SD = 1.6), 28.5%

had 10 or fewer years of education, and the average NART-r IQ was 112.5 (SD = 11). All subjects had at least one established dementia risk factor, the most prevalent being subjective memory complaints (68.9% in women; 70.1% men – see **Figure 3.1** for further details). There were no significant demographic or cognitive differences between the groups at baseline (see **Table 3.1**).

Strength and durability of effects on Global Cognition

Linear mixed-modelling repeated-measures ITT analysis revealed an overall significant Group X Time interaction on GC favouring CCT across the 15-month trial period (F-value=3.297, p=0.006). As shown in **Figure 3.3**, GC improved significantly from baseline in the CCT group compared to AC after nine sessions (FU1: Net Effect Size, NES=0.33). The effect increased after 27 additional sessions (FU2: NES=0.49). This gain diminished by about one-third three weeks after cessation (FU3: NES=0.32), but a significant medium-sized effect was maintained three months post training (FU4: NES=0.30). A small NES was noted one year after training finished (FU4: NES=0.21).

Table 3.1. Baseline characteristics.

Demographics	**CCT (n = 39)**	**AC (n=38)**	**P -value**
Age (years)	72.2 (7.1)	71.9 (5.3)	.815
Female Sex, No. (%)	29 (74)	24 (63)	.289
Native English Speakers, No. (%)	30 (78)	29 (76)	.950
NART-r (SD) pFSIQ*	112.6 (10.1)	112.3 (11.0)	.896
Prior computer use	35 (89.7)	36 (94.7)	.414
Dementia risk factors			
Subjective memory complaints†, No. (%)	27 (69.2)	27 (71.1)	.861
Hypertension, No. (%)	12 (30.8)	20 (52.6)	.052
Hypercholesterolemia, No. (%)	14 (35.9)	14 (36.8)	.931
Diabetes, No. (%)	1 (2.6)	5 (13.2)	.083
Ischemic Heart Disease, No. (%)	2 (5.1)	6 (15.8)	.125
Atrial Fibrillation, No. (%)	3 (7.7)	4 (10.5)	.665
Physical inactivity‡, No. (%)	10 (25.6)	11 (28.9)	.802
Low education (≤10 years), No. (%)	11 (28.2)	11 (28.9)	.501
Family history, No. (%)	8 (20.5)	9 (23.7)	.789
Past smoking, No. (%)	23 (59.0)	21 (55.3)	.742
Current smoking, No. (%)	2 (5.1)	0 (0)	.157
DRFS (SD)	3.0 (1.6)	3.44 (1.6)	.221
Clinical			
IQCODE score (SD)	3.05 (0.12)	3.1 (0.13)	.111
GPCOG examination score (SD)	7.92(1.3)	8.05 (1.0)	.631
MMSE (SD)	28.2 (1.4)	27.8 (1.8)	.267
B-ADL (SD)	1.58 (0.52)	1.63 (0.65)	.702
GDS (15-item) (SD)	1.7 (1.4)	1.3 (1.5)	.225
Quality of life			
QOLS (SD)	88.8 (9.8)	89.7 (9.2)	.690
SF36 physical component (SD)	72.0 (18.0)	74.6 (17.4)	.522
SF36 mental component (SD)	83.0 (9.9)	82.6 (11.1)	.868

Data are n (%) or mean (SD). DRFS=dementia risk factor score. GDS=geriatric depression scale. IQCODE=informant questionnaire on cognitive decline in the elderly. GPCOG=general practitioner assessment of cognition. MMSE=mini mental state examination. NART=national adult reading test (revised). B-ADL=Bayer activities of daily living. QOLS=quality of life scales. SF36=short form health survey. *IQ-equivalent. † defined as 4 points or less in the GPCOG questionnaire(52). ‡ defined as CHAMPS (51) estimated caloric all cause activity score <1843.

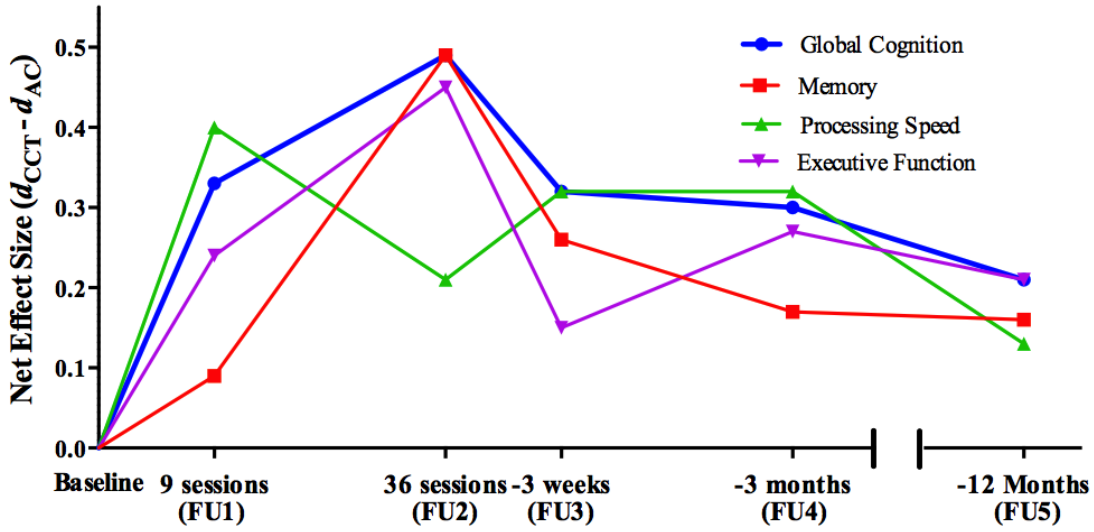


Figure 3.2: Net effect sizes (NES) for domain summary scores across the 15-month trial period as measured after 9 and 36 training sessions (FU1 and 2, respectively), as well as 3, 12 and 52 weeks after stopping training (FU3-5). NES calculated as Cohen's d [(post mean -pre mean) ÷ pooled baseline standard deviation] for CCT minus AC group, and then applying a bias correction factor (1-(3÷4[(n_{CCT} – n_{AC} – 2) – 1]) [51].

To further evaluate whether change in language abilities affect the observed efficacy on GC, on a *post hoc* basis we computed a more expansive Global Cognition Score that included two language domain tests, as well as additional memory and executive function tests that were administered only at follow-ups 2, 4 and 5 because of lack of alternate forms (see Methods section). The overall Group X Time interaction remained significant (F-value=9.004, $p<0.001$), and produced stronger effect size estimates at specified timepoints (FU2 NES = 0.65; FU4 NES=0.47; FU5 NES=0.36).

Domain-specific effects

Linear mixed-modeling repeated-measures ITT analyses revealed significant Group X Time interactions favouring CCT on two of four composite scores, namely, the memory domain ($p=0.011$) and the processing speed domain ($p=0.037$), as well as a trend on the language domain ($p=0.067$). There were no significant findings for the executive function domain (see **Table 3.2**).

Dose Response and Decay of CCT Therapeutic Effects

As opposed to GC, the effect on memory domain (see **Figure 3.3** and **Figure 3.4)** was negligible after nine sessions (FU1: NES=0.09), but reached a similar effect to GC after 36 sessions (FU2: NES=0.49). These gains more than halved three weeks after stopping training (FU3: NES=0.26) and continued to diminish one year later (FU4: NES=0.17; FU5: NES=0.16). CCT effects on the processing speed domain showed a unique pattern (**Figure 3.3** and **Figure 3.4)**. The therapeutic effect peaked after nine sessions (FU1: NES=0.40), and then declined after 36 sessions (FU2: NES=0.21). However, medium-sized effects favouring CCT were maintained throughout the three-month post training period (FU3: NES=0.49; FU4: NES=0.32), diminishing by approximately a half one-year after training stopped (FU5: NES=0.13).

Longitudinal effect on activities of daily living

One year after training cessation there was no significant Group X Time interaction improvement on Bayer Activities of Daily Living scale, resulting from a small effect size in the CCT group (ES 0.20) and no change in the AC group (ES 0.00; NES=0.20, F = 0.162 p= 0.689).

Table 3.2. Cohen's d effect size for CCT and AC groups (95% confidence interval).

		CCT		AC		Bias Corrected Net ES	ITT Mixed Model TIME X GROUP	
		d	95% CI	d	95% CI		F-Value	p-value
Global Cognition	FU1	0.70	(0.24 to 1.16)	0.37	(-0.09 to 0.82)	0.33		
	FU2	1.12	(0.61 to 1.62)	0.62	(0.15 to 1.09)	0.49		
	FU3	1.19	(0.68 to 1.7)	0.87	(0.39 to 1.36)	0.32	3.297	0.006
	FU4	1.34	(0.81 to 1.86)	1.04	(0.54 to 1.53)	0.30		
	FU5	1.27	(0.72 to 1.81)	1.05	(0.54 to 1.57)	0.21		
Memory Domain	FU1	0.28	(-0.17 to 0.73)	0.20	(-0.26 to 0.65)	0.09		
	FU2	0.87	(0.38 to 1.36)	0.38	(-0.09 to 0.84)	0.49		
	FU3	0.66	(0.18 to 1.14)	0.40	(-0.07 to 0.87)	0.26	3.028	0.011
	FU4	0.68	(0.19 to 1.16)	0.51	(0.04 to 0.98)	0.17		
	FU5	0.84	(0.32 to 1.36)	0.68	(0.18 to 1.18)	0.16		
Information Processing Speed	FU1	0.62	(0.16 to 1.09)	0.22	(-0.23 to 0.67)	0.40		
	FU2	0.73	(0.23 to 1.22)	0.52	(0.05 to 0.99)	0.21		
	FU3	1.01	(0.5 to 1.52)	0.69	(0.21 to 1.16)	0.32	2.403	0.037
	FU4	1.19	(0.67 to 1.72)	0.87	(0.39 to 1.35)	0.32		
	FU5	1.00	(0.46 to 1.54)	0.86	(0.36 to 1.37)	0.13		
Executive Function Domain	FU1	0.71	(0.24 to 1.17)	0.46	(0 to 0.92)	0.24		
	FU2	0.94	(0.44 to 1.44)	0.49	(0.02 to 0.96)	0.45		
	FU3	1.02	(0.52 to 1.52)	0.87	(0.38 to 1.35)	0.15	1.036	0.397
	FU4	1.18	(0.66 to 1.69)	0.90	(0.41 to 1.4)	0.27		
	FU5	1.01	(0.48 to 1.53)	0.80	(0.3 to 1.3)	0.20		
Language Domain	FU2	0.76	(0.28 to 1.25)	0.55	(0.08 to 1.02)	0.21	2.433	0.67
	FU4	0.71	(0.22 to 1.20)	0.52	(0.08 to 0.99)	0.18		
	FU5	1.01	(0.48 to 1.54)	0.90	(0.38 to 1.41)	0.11		
Extended Global Cognition	FU2	1.24	(0.73 to 1.75)	0.59	(0.11 to 1.06)	0.65	9.004	<0.001
	FU4	1.33	(0.80 to 1.85)	0.86	(0.38 to 1.34)	0.47		
	FU5	1.35	(0.80 to 1.89)	0.98	(0.47 to 1.49)	0.36		

Bias-corrected net effect size (NES) is difference between two effects after correction. F-value refers to linear mixed model with Time (six repeated measures), Group and Group X Time terms in model. P-value refers to Group X Time interaction.

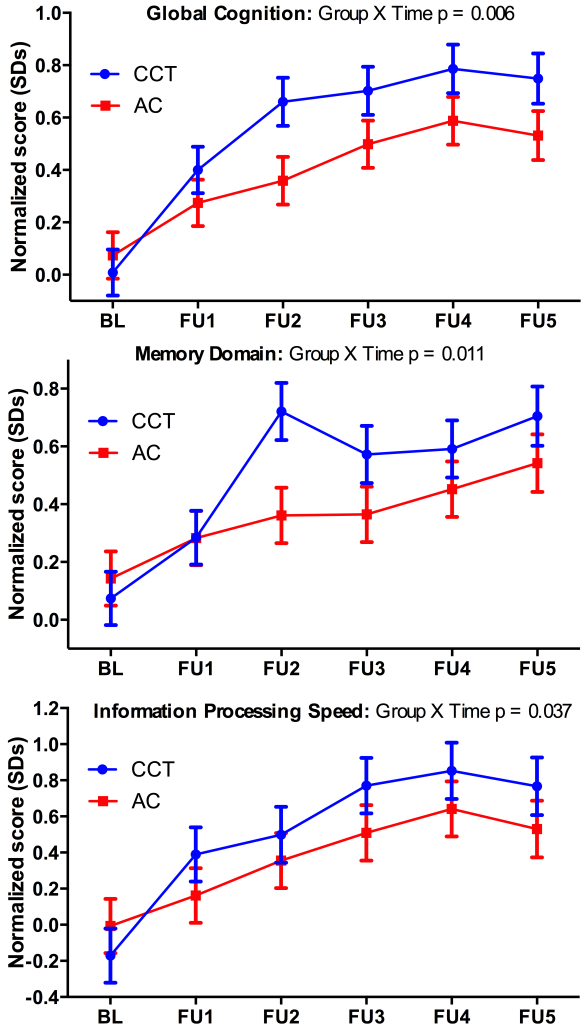


Figure 3.4: Mean change on GC, memory and information processing speed across the six time points. CCT=computerized cognitive training. AC=active control. FU1=after 9 training sessions. FU2=after 36 training sessions. FU3=3 weeks after cessation. FU4=12 weeks after cessation, FU5=52 weeks after cessation. Graphs depict change from baseline in SD units based on ITT MMRM estimated marginal means ±SEM.

3.4 Discussion

To the best of our knowledge this is the first randomized, double-blind, active-controlled trial to demonstrate efficacy of computerised cognitive training on GC in non-impaired older adults[27,52]. The magnitude of the net effect size at the end of 36 hours of training is sufficient (NES 0.49) to be of clinical interest. Some of these benefits were preserved as far out as 12 months after completing training, but as expected, decayed relative to combined retest and non-specific effects in the active control group. This comparison group was the most rigorous implemented thus far, designed to take into account of sensorimotoric, mnemonic,

attentional, motivational, social and trainer-related stimulation. In addition, we chose outcome measures with multiple available forms that were functionally dissimilar to the CCT exercises, and analysed results on cognitive composite scores rather than individual tests, further increasing their reliability[6]. For the first time, we also examined cognitive outcomes at multiple time points during and after CCT, providing new insights into dose-response relationships. Memory effects for example continue to display a steep upward trajectory even after 36 training sessions, but decay rapidly following training offset, in contrast to processing speed effects which peak after 9 sessions but then are largely resistant to decay for at least 3 months following the end of training.

Previous trials of *non-computerized* cognitive interventions have reported improved GC in healthy and mildly impaired older adults[53-56], however, these employed single-blinded wait-list control designs and multi-faceted interventions that make interpretation difficult[39,57]. Notably, the NES in these trials were considerably smaller than reported here under more rigorous conditions. Interestingly, three recent well-designed RCTs in the elderly have failed to detect GC effects following CCT[27,58,59]. Similar to our study, these used multi-domain CCT and a comparable number of training sessions, but unlike our study, CCT was self-administered at home rather than in a supervised group setting. This raises the possibility that expert supervision involving feedback, motivational support and emphasis of applicability of training to everyday life may be a key factor moderating CCT outcomes[60,61], as clearly supported by the moderator analysis in **Chapter 2**.

For the first time, we also examined cognitive outcomes at multiple time points during and after CCT, providing new insights into dose-response relationships. Memory effects for example continue to display a steep upward trajectory even after 36 training sessions, but decay rapidly following training offset, in contrast to processing speed effects which peak

after 9 sessions but then are largely resistant to decay for at least 3 months following the end of training. This information may help develop more effective CCT software in the future. Moreover, the fact that CCT has effected memory and processing speed but not language and executive function is completely consistent with the results of **Chapter 2**.

The issue of which CCT software package is optimal for enhancing GC in this population remains open in the absence of head-to-head RCTs. We used COGPACK, which has a relatively rich history within the cognitive rehabilitation setting [62] and is convenient for research purposes. However, COPGACK relies on now dated technology that lacks useful auditory exercises and relies on a trainer rather than an automated algorithm to create the training regimen and adapt training content. Accordingly, there is great scope for improving beyond these reported outcomes with new software that takes into account underlying dose-response functions.

It is also important to note that whilst efficacy on GC may be a necessary condition for primary dementia prevention, it is not sufficient. For this purpose, robust and simultaneous effects on daily function are required [23]. We found only small and non-significant effects using the Bayer ADL measure at our 12-month post training assessment (NES=0.2); based on these results 80% power would require a total final sample size of 787. This finding is therefore in line with the weak IADL effects (NES=0.29) found in the large ACTIVE trial following paper-and-pencil reasoning training[63]. The overarching clinical challenge for CCT researchers is therefore to demonstrate far transfer to everyday function, an issue closely related to development of validated tools sensitive enough to detect treatment-related functional change in asymptomatic and preclinical individuals[37].

For the full anti-brain-aging potential of CCT to be realised evidence needs to move beyond simple efficacy to understanding fundamental therapeutic characteristics. We found that

supervised, centre-based, multidomain CCT is effective at improving global cognitive performance in older individuals over the long term, and moreover, this outcome was based on a complex pattern of dose-dependent gains during training and time-dependent decay following training offset. This information will be vital to the design of next generation CCT technology, as well as for helping clinicians and researchers make the most this intervention.

References

1. Beddington J, Cooper CL, Field J, et al. The mental wealth of nations. *Nature*. 2008;455(7216):1057–1060. doi:10.1038/4551057a.

2. Cullum S, Huppert FA, McGee M, et al. Decline across different domains of cognitive function in normal ageing: results of a longitudinal population-based study using CAMCOG. *Int J Geriatr Psychiatry*. 2000;15(9):853–862.

3. Tucker-Drob EM. Global and domain-specific changes in cognition throughout adulthood. *Dev Psychol*. 2011;47(2):331–343. doi:10.1037/a0021361.

4. Dregan A, Stewart R, Gulliford MC. Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. *Age Ageing*. 2013;42(3):338–345. doi:10.1093/ageing/afs166.

5. Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. *Nat Rev Neurosci*. 2004;5(2):87–96. doi:10.1038/nrn1323.

6. Salthouse TA. Robust cognitive change. *J Int Neuropsychol Soc*. 2012;18(4):749–756. doi:10.1017/S1355617712000380.

7. Buschert V, Bokde ALW, Hampel H. Cognitive intervention in Alzheimer disease. *Nat Rev Neurol*. 2010;6(9):508–517. doi:10.1038/nrneurol.2010.113.

8. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*. 2012;37(1):43–76. doi:10.1038/npp.2011.251.

9. Lustig C, Shah P, Seidler R, Reuter-Lorenz PA. Aging, training, and the brain: a review and future directions. *Neuropsychol Rev*. 2009;19(4):504–522. doi:10.1007/s11065-009-9119-9.

10. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*. 2011;(1):CD006220. doi:10.1002/14651858.CD006220.pub2.

11. Middleton LE, Yaffe K. Targets for the prevention of dementia. *J Alzheimers Dis*. 2010;20(3):915–924. doi:10.3233/JAD-2010-091657.

12. Wilson RS, Segawa E, Boyle PA, Anagnos SE, Hizel LP, Bennett DA. The natural history of cognitive decline in Alzheimer's disease. *Psychol Aging*. 2012;27(4):1008–1017. doi:10.1037/a0029857.

13. Christensen K, Thinggaard M, Oksuzyan A, et al. Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *Lancet*. 2013. doi:10.1016/S0140-6736(13)60777-1.

14. Burdick DJ, Rosenblatt A, Samus QM, et al. Predictors of functional impairment in residents of assisted-living facilities: the Maryland Assisted Living study. *J Gerontol A Biol Sci Med Sci*. 2005;60(2):258–264.

15. Burton CL, Strauss E, Hultsch DF, Hunter MA. Cognitive functioning and everyday problem solving in older adults. *Clin Neuropsychol*. 2006;20(3):432–452. doi:10.1080/13854040590967063.

16. Schmidt FL, Hunter J. General mental ability in the world of work: occupational attainment and job performance. *J Pers Soc Psychol*. 2004;86(1):162–173. doi:10.1037/0022-3514.86.1.162.

17. Buchman AS, Boyle PA, Leurgans SE, Barnes LL, Bennett DA. Cognitive function is associated with the development of mobility impairments in community-dwelling elders. *Am J Geriatr Psychiatry*. 2011;19(6):571–580. doi:10.1097/JGP.0b013e3181ef7a2e.

18. Davis JD, Papandonatos GD, Miller LA, et al. Road test and naturalistic driving performance in healthy and cognitively impaired older adults: does environment matter? *J Am Geriatr Soc*. 2012;60(11):2056–2062. doi:10.1111/j.1532-5415.2012.04206.x.

19. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299–308. doi:10.1093/ageing/afs012.

20. Sheehan B. Assessment scales in dementia. *Ther Adv Neurol Disord*. 2012;5(6):349–358. doi:10.1177/1756285612455733.

21. Andrieu S, Coley N, Aisen P, et al. Methodological issues in primary prevention trials for neurodegenerative dementia. *J Alzheimers Dis*. 2009;16(2):235–270. doi:10.3233/JAD-2009-0971.

22. Kivipelto M, Solomon A, Ahtiluoto S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimers Dement*. 2013. doi:10.1016/j.jalz.2012.09.012.

23. Kurz AF, Leucht S, Lautenschlager NT. The clinical significance of cognition-focused interventions for cognitively impaired older adults: a systematic review of randomized controlled trials. *Int Psychogeriatr*. 2011:1–12. doi:10.1017/S1041610211001001.

24. Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *N Engl J Med*. 2013;368(13):1169–1171. doi:10.1056/NEJMp1302513.

25. Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: a systematic review. *PLoS ONE*. 2012;7(7):e40588. doi:10.1371/journal.pone.0040588.

26. Jak AJ, Seelye AM, Jurick SM. Crosswords to computers: a critical review of popular approaches to cognitive enhancement. *Neuropsychol Rev*. 2013;23(1):13–26. doi:10.1007/s11065-013-9226-5.

27. Barnes DE, Santos-Modesitt W, Poelke G, et al. The Mental Activity and eXercise (MAX) Trial: A Randomized Controlled Trial to Enhance Cognitive Function in Older Adults. *JAMA Intern Med*. 2013;173(9):797–804. doi:10.1001/jamainternmed.2013.189.

28. Bozoki A, Radovanovic M, Winn B, Heeter C, Anthony JC. Effects of a computer-based cognitive exercise program on age-related cognitive decline. *Arch Gerontol Geriatr*. 2013;57(1):1–7. doi:10.1016/j.archger.2013.02.009.

29. van Muijden J, Band GPH, Hommel B. Online games training aging brains: limited transfer to cognitive control functions. *Front Hum Neurosci*. 2012;6:221. doi:10.3389/fnhum.2012.00221.

30. Wilson RS, Beckett LA, Barnes LL, et al. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging*. 2002;17(2):179–193.

31. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. *N Engl J Med*. 2003;348(25):2508–2516. doi:10.1056/NEJMoa022252.

32. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, Verghese J. Cognitive activities delay onset of memory decline in persons who develop dementia. *Neurology*. 2009;73(5):356–361. doi:10.1212/WNL.0b013e3181b04ae3.

33. Valenzuela M, Brayne C, Sachdev P, Wilcock G, Matthews F, Medical Research Council Cognitive Function and Ageing Study. Cognitive lifestyle and long-term risk of dementia and survival after diagnosis in a multicenter population-based cohort. *Am J Epidemiol*. 2011;173(9):1004–1012. doi:10.1093/aje/kwq476.

34. Marioni RE, Valenzuela MJ, van den Hout A, Brayne C, Matthews FE, MRC Cognitive Function and Ageing Study. Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS ONE*. 2012;7(12):e50940. doi:10.1371/journal.pone.0050940.

35. Unverzagt FW, Guey LT, Jones RN, et al. ACTIVE cognitive training and rates of incident dementia. *J Int Neuropsychol Soc*. 2012;18(4):669–677. doi:10.1017/S1355617711001470.

36. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271–2281.

37. Zelinski EM. Far transfer in cognitive training of older adults. *Restor Neurol Neurosci*. 2009;27(5):455–471. doi:10.3233/RNN-2009-0495.

38. Anguera JA, Boccanfuso J, Rintoul JL, et al. Video game training enhances cognitive control in older adults. *Nature*. 2013;501(7465):97–101. doi:Letter.

39. Boot WR, Simons DJ, Stothart C, Stutts C. The Pervasive Problem With Placebos in Psychology: Why Active Control Groups Are Not Sufficient to Rule Out Placebo Effects. *Perspect Psychol Sci*. 2013;8(4):445–454.

40. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, Ritter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Med Sci Sports Exerc*. 2001;33(7):1126–1141.

41. Brodaty H, Pond D, Kemp NM, et al. The GPCOG: a new screening test for dementia designed for general practice. *J Am Geriatr Soc*. 2002;50(3):530–534.

42. Gates NJ, Valenzuela M, Sachdev PS, et al. Study of Mental Activity and Regular Training (SMART) in at risk individuals: a randomised double blind, sham controlled, longitudinal trial. *BMC Geriatr*. 2011;11:19. doi:10.1186/1471-2318-11-19.

43. Dwolatzky T, Whitehead V, Doniger GM, et al. Validity of a novel computerized cognitive battery for mild cognitive impairment. *BMC Geriatr*. 2003;3:4. doi:10.1186/1471-2318-3-4.

44. Snyder PJ, Jackson CE, Petersen RC, et al. Assessment of cognition in mild cognitive impairment: a comparative study. *Alzheimers Dement*. 2011;7(3):338–355. doi:10.1016/j.jalz.2011.03.009.

45. Robbins TW, James M, Owen AM, et al. A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. *J Int Neuropsychol Soc*. 1998;4(5):474–490.

46. Loonstra AS, Tarlow AR, Sellers AH. COWAT metanorms across age, education, and gender. *Appl Neuropsychol*. 2001;8(3):161–166. doi:10.1207/S15324826AN0803_5.

47. Graves RE, Bezeau SC, Fogarty J, Blair R. Boston naming test short forms: a comparison of previous forms with new item response theory based forms. *J Clin Exp Neuropsychol*. 2004;26(7):891–902. doi:10.1080/13803390490510716.

48. Warrington EK. Manual for the Recognition Memory Test for words and faces. *Windsor, UK: NFER-Nelson*. 1984.

49. Hindmarch I, Lehfeld H, de Jongh P, Erzigkeit H. The Bayer Activities of Daily Living Scale (B-ADL). *Dement Geriatr Cogn Disord*. 1998;9 Suppl 2:20–26.

50. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry*. 2004;61(3):310–317. doi:10.1001/archpsyc.61.3.310.

51. Morris SB. Estimating Effect Sizes From Pretest-Posttest-Control Group Designs. *Organizational Research Methods*. 2008.

52. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. *Ageing Res Rev*. 2013;12(1):263–275. doi:10.1016/j.arr.2012.07.003.

53. Oswald W, Gunzelmann T, Rupprecht R, Hagen B. Differential effects of single versus combined cognitive and physical training with older adults: the SimA study in a 5-year perspective. *Eur J Ageing*. 2006;3(4):179–192. doi:10.1007/s10433-006-0035-z.

54. Buschert VC, Friese U, Teipel SJ, et al. Effects of a newly developed cognitive intervention in amnestic mild cognitive impairment and mild Alzheimer's disease: a pilot study. *J Alzheimers Dis*. 2011;25(4):679–694. doi:10.3233/JAD-2011-100999.

55. Tsolaki M, Kounti F, Agogiatou C, et al. Effectiveness of nonpharmacological approaches in patients with mild cognitive impairment. *Neurodegener Dis*. 2011;8(3):138–145. doi:10.1159/000320575.

56. Cheng Y, Wu W, Feng W, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. *BMC Med*. 2012;10:30. doi:10.1186/1741-7015-10-30.

57. Shumaker SA, Legault C, Coker LH. Behavior-based interventions to enhance cognitive functioning and independence in older adults. *JAMA*. 2006;296(23):2852–2854. doi:10.1001/jama.296.23.2852.

58. Barnes DE, Yaffe K, Belfor N, et al. Computer-based cognitive training for mild cognitive impairment: results from a pilot randomized, controlled trial. *Alzheimer Dis Assoc Disord*. 2009;23(3):205–210. doi:10.1097/WAD.0b013e31819c6137.

59. Peretz C, Korczyn AD, Shatil E, Aharonson V, Birnboim S, Giladi N. Computer-based, personalized cognitive training versus classical computer games: a randomized double-blind prospective trial of cognitive stimulation. *Neuroepidemiology*. 2011;36(2):91–99. doi:10.1159/000323950.

60. Phye GD. Advice and feedback during cognitive training: Effects at acquisition and delayed transfer. *Contemporary Educational Psychology*. 1991;16(1):87–94. doi:doi:10.1016/0361-476X(91)90008-9.

61. Cavallini E, Dunlosky J, Bottiroli S, Hertzog C, Vecchi T. Promoting transfer in memory training for older adults. *Aging Clin Exp Res*. 2010;22(4):314–323. doi:10.3275/6704.

62. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry*. 2011;168(5):472–485. doi:10.1176/appi.ajp.2010.10060855.

63. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006;296(23):2805–2814. doi:10.1001/jama.296.23.2805.

Chapter 4: Timecourse of CCT-induced structural and functional brain plasticity: A Pilot Study

Introduction

Throughout the past decade neuroimaging studies of CT studies have been influential in providing an insight into the human brain's neuroplasticity, and hence helped reform longstanding attitudes about the inevitability of degeneration and decline in late life. As the field moves from traditional 'does brain training work?' about the questions to more detailed investigation about the mechanisms of action[1] and optimised practice parameters, neuroimaging may have several roles to play[2-4]:

First, the main evidence base for the field is centred around neuropsychological measures of cognition (see **Chapter 2**), and so there remains an absence of a solid neurobiological theory for clinical effectiveness, something that can only be established when several studies are able to show consistent links between cognitive change and measures of structural and functional brain adaptation. Second, imaging can help determine whether CT reverses or attenuates longitudinal patterns of degeneration or age-associated neurobiological dysfunction. Third, neuroimaging have help identify 'brain-training responsive brains', that is, multivariate neuroimaging patterns at baseline that can distinguish between those individuals that will have a robust clinical response to training from those who will not. Finally, development of new CT exercises could be immensely enhanced by looking at neuroplastic processes stimulated by specific exercises, feeding this back into exercise development in an iterative cycle.

Alas, a number of methodological challenges will need to be solved before neuroimaging can fulfil these roles. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are currently too expensive to become common endpoints in clinical trials, and standards of image processing, analysis and reporting need to be improved[5]. Importantly, *in vivo* imaging is not yet sensitive enough to detect changes at the molecular and cellular scale, as well as other likely relevant microstructural processes such as neurogenesis and angiogenesis[6]. The same problem exists in regard to quantitate electroencephalography (qEEG), which, despite its relative simplicity (notably the ability to record task-dependent cortical activity for a long duration without having to lay in a scanner), and low cost, it has yet to be established as a reliable and sensitive brain imaging technique[6,7].

Notwithstanding these challenges, at least eight controlled trials have demonstrated CT-induced brain plasticity in healthy elderly using MRI[8-15] (see also a review by Suo and Valenzuela[2]), and a similar number of studies have done so in subjects with MCI[3]. In addition, at least two well designed studies have used qEEG to study specific CCT tasks in healthy elderly[16,17], and an array of imaging studies have used MRI outcomes to study CT effects in neuropsychiatric populations (reveiwed by Vinogradov et al[4]).

To date neuroimaging studies of CT have used inconsistent methods and present a heterogeneous body of evidence (like the clinical studies reviewed in **Chapter 2**). To the best of our knowledge, no study has yet reported null effects of CT on any neuroimaging outcomes, with the literature populated only by positive results, clearly ignoring or underreporting statistically insignificant results. There is therefore strong reason to believe that the current literature is biased.

As part of the Timecourse Trial (**Chapter 3**) we therefore designed and conducted a pilot investigation to examine the utility of MRI measures of multidomain CCT-induced neuroplasticity. More specifically, we aimed to 1) pilot test multimodal neuroimaging to assess evidence for mediating mechanisms of global cognition gains, and 2) compare effect sizes from cognitive measures to those generated from neuroimaging in order to assess their potential role as endpoints for CCT trials. All procedures and analyses were conducted as predetermined, with an emphasis on using the most recent data acquisition, processing and analysis tools and testing for relationships with cognitive outcomes.

Methods

4.1.1 Study Design and Participants

This study was conducted using a subsample of participants from the Timecourse Trial, using the same recruitment, eligibility criteria, randomisation, interventions and assessment methods. After giving their consent to participate in the trial, participants in whom MRI was not contraindicated (e.g., no metallic implants) were offered to participate in the imaging subsample in addition to the main trial. Neither consent nor refusal to participate in the imaging subsample affected inclusion, randomisation, intervention or cognitive assessments, and cognitive data from participants in the imaging subsample was combined with those of the other participants. Inclusion in the subsample was determined after randomisation to the main trial based on a 2:1 allocation with N = 18, i.e., the first twelve participants from the CCT group and first six participants from the AC group who consented to participate in the imaging subsample were included in this study.

The Timecourse Trial (**Chapter 3**) was a randomised active-controlled trial of centre-based multidomain CCT in healthy older adults. After baseline assessment, eligible participants received a total dose of 36 one-hour session of either CCT or an active control intervention. Additional cognitive assessments were conducted after 9 hours (follow-up 1) and 36 hours of training (follow-up 2). Three longitudinal assessments were performed 3 weeks, 3 months and 12 months after training cessation. Primary outcomes were global cognition, as well as composite scores of memory, information processing speed, executive functioning and language.

4.1.2 Data Acquisition

Multimodal MRI scans were performed on three occasions, at baseline, after nine training sessions (FU1) and after 36 sessions (FU2), using a 3.0-Tesla General Electric scanner at the Brain and Mind Research Institute, University Of Sydney. Each scan took 45-50 minutes to complete and included:

1 Structural (sMRI): 3D, T1-weighted whole brain scan (sequence: T1GR; TR/TE 7.1/2.7ms; slice thickness 1mm without gaps; field of view 256x256; resolution 1x1mm.

2 Resting-state fMRI: T2* echo-planar BOLD sequence (T2*EP/RG; TR/TE 2000/30; slice thickness 4.5mm without gaps; 200 volumes, 6.5 minutes), eyes closed.

3 Proton Magnetic Resonance Spectroscopy (1H-MRS): in left hippocampus (20mm M/L, 15mm D/V, 30mm A/P, oriented along the hippocampus) and posterior cingulate grey matter (20mm M/L, 20mm D/V, 30mm A/P) using the PRESS sequence (TE/TR 20/2000ms, 1024 points, 256 averages).

4 Diffusion Tensor Imaging (DTI): 40 directions, TR/TE 10293/55ms, 60 slices, 2mm3 isotropic.

4.2.3 MRI Preprocessing

sMRI. Two structural analyses were used. First, we performed VBM longitudinal preprocessing pipeline as per our previously published protocol[18] using SPM version 8 (Wellcome Trust Centre for Neuroimaging, London, UK) running on Matlab 2012a (MatWorks Inc., Natick, MA). Intra-subject image normalisation was performed for the three timepoints (BL, FU1, FU2) combined. Secondly, an analysis of cortical structures was performed using the longitudinal pipeline of FreeSurfer[19]. It creates a within-subject template through a variety of steps including image registration, normalization, skull-stripping, segmentation of grey and white matter, and delineation between the inner grey-white matter and outer pial surface. The resulting surface maps where then used to assess the longitudinal training effect, at both a whole-brain (QDEC) and regional level (parcellation), with changes in cortical thickness indicative of structural neuroplasticity.

fMRI. Resting-state fMRI data were preprocessed using the Data Processing Assistant for Resting State fMRI toolbox of the SPM8, normalised to standard MNI space and smoothed using 8mm kernel. The Resting State fMRI Data Analysis Toolkit (REST, www.restfmri.net) was used to generate pre-specified seed-wise functional connectivity (FC) maps of the *hippocampus* and the *posterior cingulate*. Nuisance variables related to white matter, whole-brain and CSF signal and head motion were regressed out along with 6 co-registration factors. Individual FC maps for each seed and FU were based on voxel-wise correlations between the mean signal

of the seed and other regions, and then transformed into z-scores. Baseline FC maps for the whole sample are presented in **Figures 4.1** and **4.2** below.

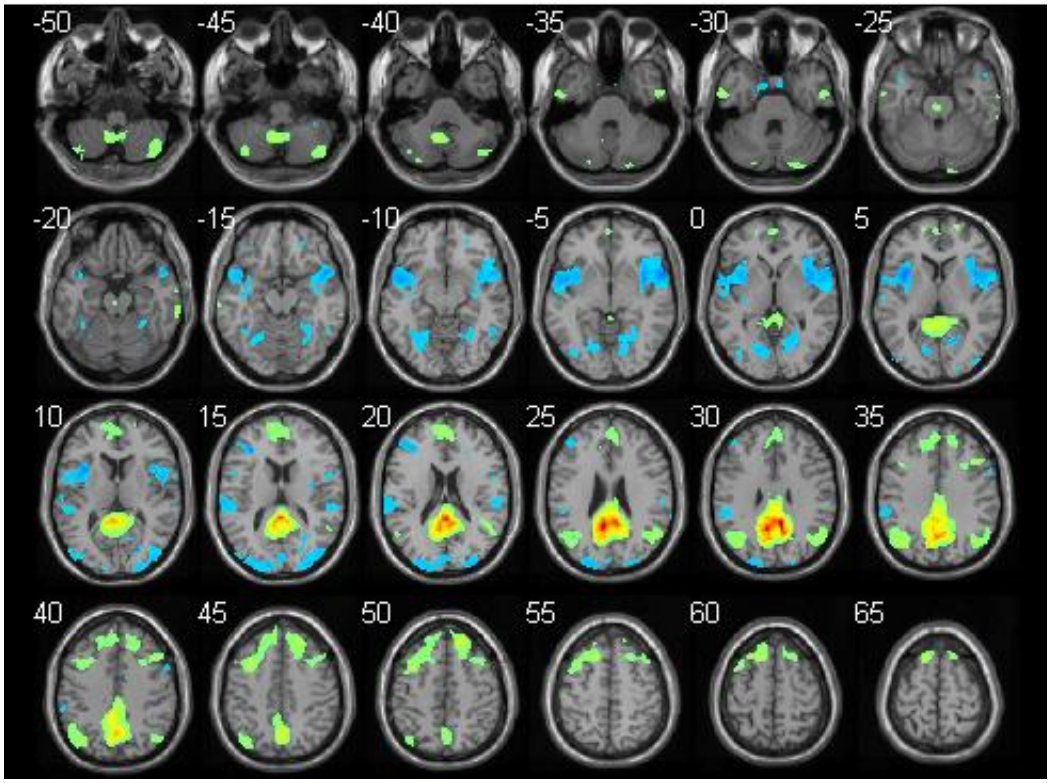


Figure 4.1: Baseline whole-brain functional connectivity map for the posterior cingulate seed (t = 3.93, df = 12, p = 0.001, cluster size threshold =5) on a standardised single T1 template. Hot areas represent voxels positively correlated with the seed and cool areas negative correlations.

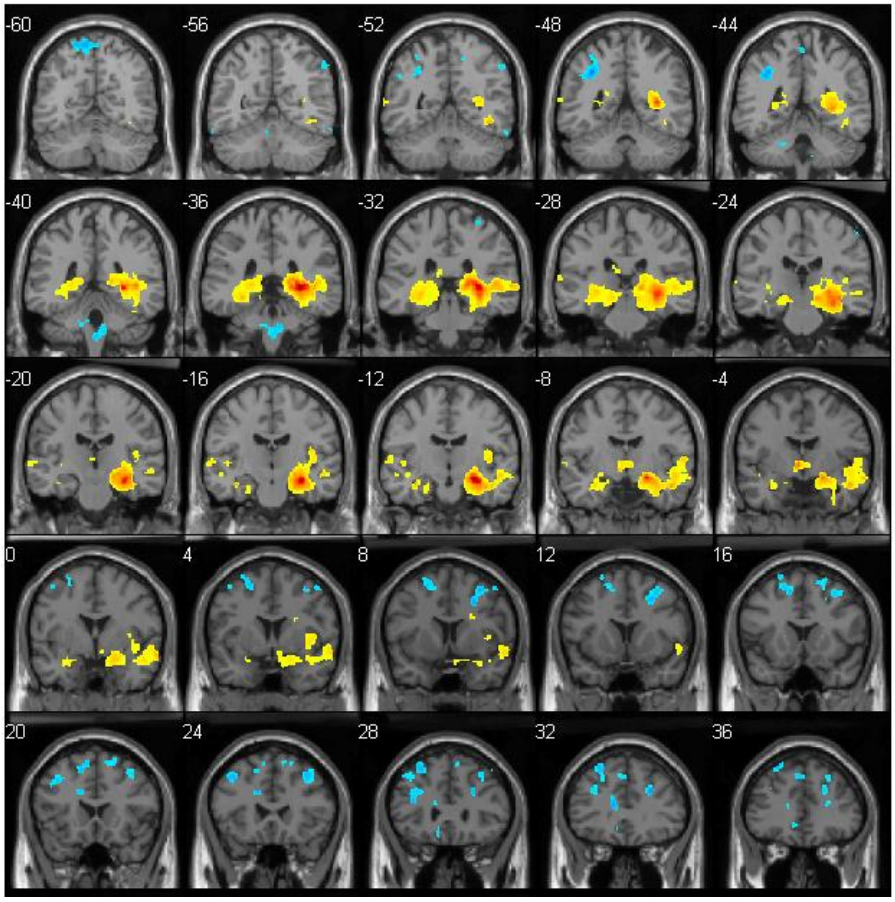


Figure 4.2: Baseline whole-brain functional connectivity map for the right hippocampus seed (t = 3.93, df = 11, p = 0.001176, cluster size threshold =5) on a standardised single T1 template. Hot areas represent voxels positively correlated with the seed and cool areas negative correlations.

1H-MRS. We followed our previously published protocols for MRS processing of the five main metabolite signals[8,20,21] namely N-acetylaspartate (NAA), Creatine (Cr), Cholines (Cho) Myo-inositol (mI) and Glutamate+Glutamine (Glx). Residual water signal was first removed by Hankel Lanczos Squares Singular Value Decomposition filter. The spectra were then aligned by setting NAA peak to 2.02ppm and baseline correction performed (using 150 data points for mean). Finally, we used the AMARES jMRUI procedure to quantify the amplitudes of the five metabolite peaks and calculated relative amplitudes using Creatine as reference peak.

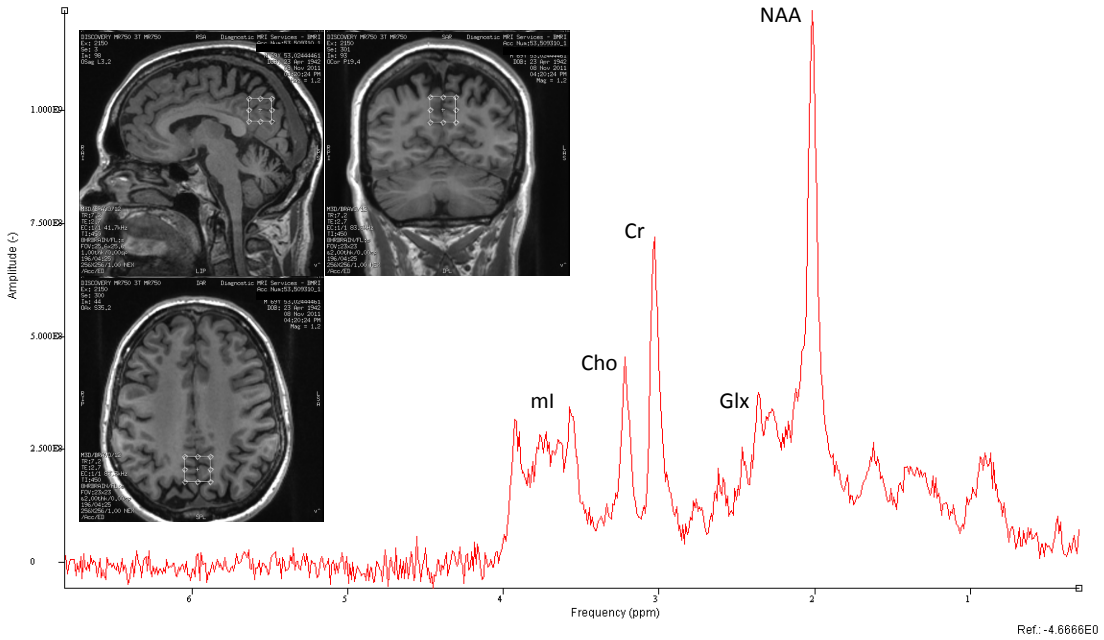


Figure 4.3: Example of ROI placement and baseline spectra – posterior cingulate.

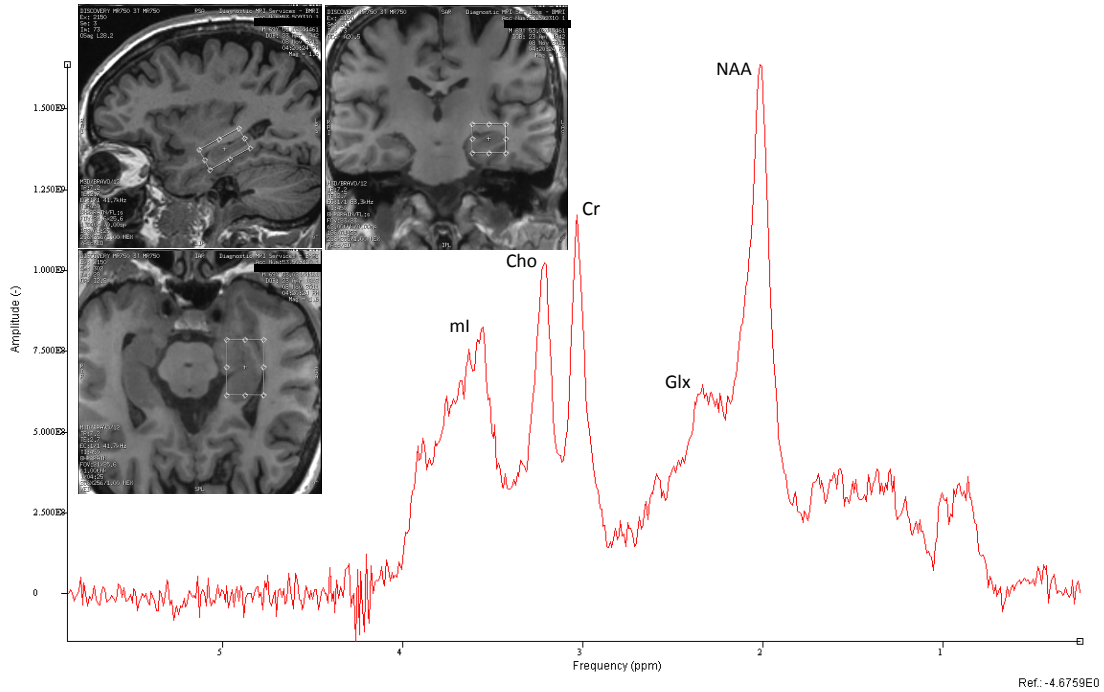


Figure 4.4: Example of ROI placement and baseline spectra – left hippocampus.

DTI. Fractional anisotropy (FA) data were preprocessed using the Tract-Based Spatial Statistics (TBSS) script of the FSL suit, using published methods[22]. Very briefly, TBSS aligns all FA images to a mean FA skeleton, and generates individual FA data as a projection onto the mean skeleton.

4.2.4 Postprocessing and Statistical Analyses

Voxel-based analyses. A longitudinal general linear model was used to analyse the structural VBM-preprocessed and resting state fMRI FC-map data. Both analyses were based on a flexible factorial design with three factors (subject, group and time) and one interaction (group X time), correcting at the whole-brain cluster-level using a false discovery rate (FDR) procedure at the $p<0.05$ level. Finally, statistically significant results were correlated with changes in global cognition (GC) scores in the imaging subsample.

Vertex-based analysis. Vertex-based analysis was conducted on the outputs from the FreeSurfer longitudinal pipeline, using the FreeSurfer QDEC toolbox. Three measures of cortical thickness change were used to assess for plasticity, namely: 1) annualised rate of change (+/-) in mm/year, 2) symmetrised percent change (SPC) with respect to the temporal average, and 3) percentage change with respect to baseline (PCL). A longitudinal general linear model was used with group as the main factor. Multiple comparisons were corrected using two methods, namely: whole-brain vertex based FDR correction, and exploratory small-volume based FDR correction.

MRS and FA analyses. Preprocessed data was analysed using linear mixed-modeling repeated-measures analyses, with Group and Time as main factors and the interaction of interest (Group x Time) on SPSS 20. All group x time interactions tested changes from baseline to FU1 or change from baseline to FU2.

4.3 Results

Eighteen subjects were initially included in the imaging subsample. Three withdrew consent between baseline and FU1 and one passed away between FU1 and FU2. Two additional subjects withdraw consent from the imaging subsample but completed the main trial, and one subject was excluded from the trial following pathological findings in his baseline MRI scan (diagnosed with Parkinson's disease soon after). A total of 12 subjects (CCT: six females, one male; AC: five males, mean age 71.4) were therefore analysed on a per-protocol completion basis, using three scans per subject.

VBM whole brain analysis. After FDR correction for multiple comparisons there was a significant group x time interaction in the right *postcentral gyrus* (t=4.6, k_E=1122, p_{corr} = 0.003, peak at xyz 39 -25 60) in the CCT group compared to an observed shrinkage in that region in the AC group from baseline to both FU1 (z_{CCT}=0.39; z_{AC}=-0.34) and FU2 (z_{CCT}=0.66; z_{AC}= -0.53). See **Figure 4.5** for a representation of these results. In addition, there was a significant group x time interaction in the right *fusiform gyrus* (t=4.53, k_E=1711, p_{corr}<0.001, peak at 39 -40 -5, see **Figure 4.6**). Across the entire sample, there were significant positive correlations between changes in the postcentral gyrus and change in global cognition at both FU1 and FU2 (see **Figure 4.5**).

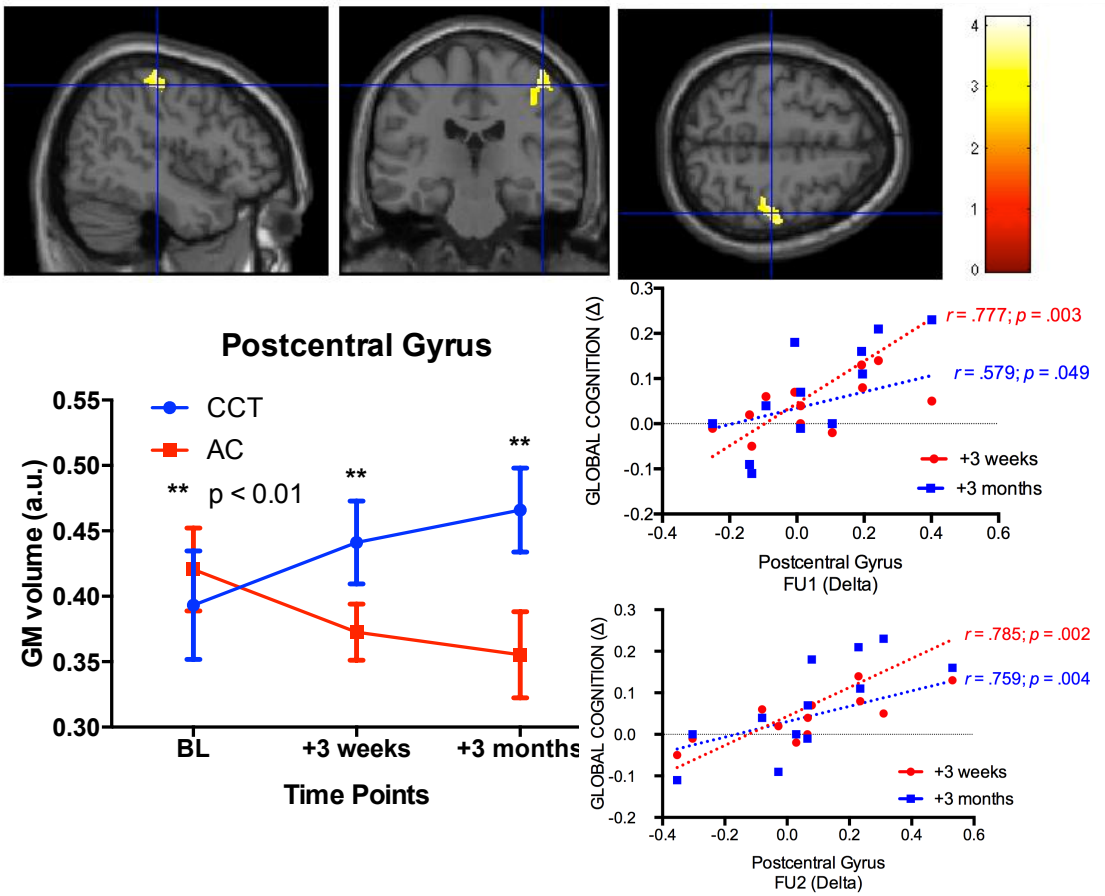


Figure 4.5: VBM changes in the postcentral gyrus at FU1 (+3weeks) and correlations with change in global cognition at the same timepoint (+3weeks) and at a delayed timepoint (+3months).

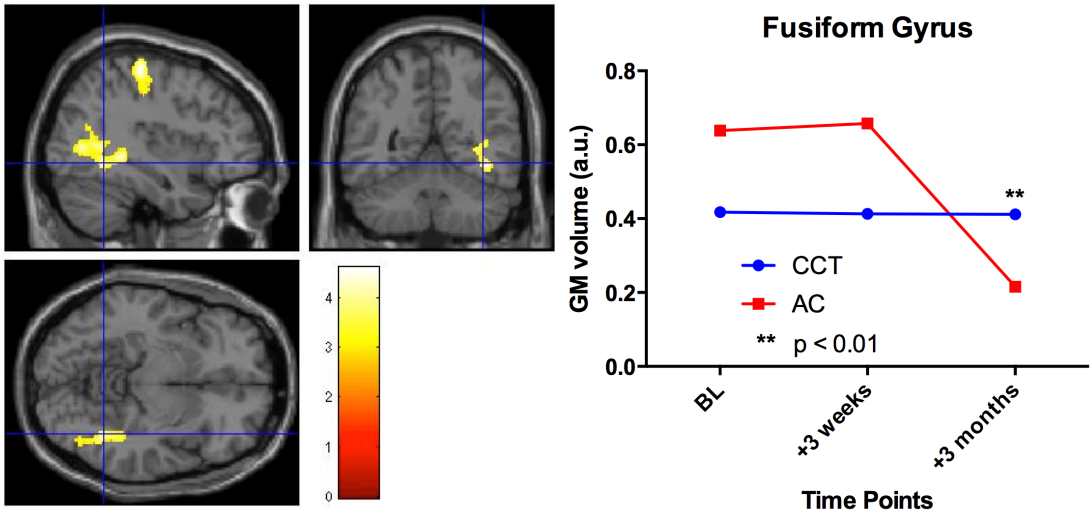


Figure 4.6: Changes in the Fusiform gyrus (VBM)
(Note: no correlations between VBM changes in the fusiform gyrus and GC changes were found).

Vertex-based analysis. Whole-brain correction did not yield any suprathreshold results, but two regions were identified for further exploration using small volume correction. After small volume correction, there was a significant between-group difference in rate of thickness change between baseline and FU2 in the *left fusiform gyrus* (voxel/vertex-wise threshold [vwth] = 3.39, $p < 0.001$, see **Figure 4.7**), as well as a large cluster in the right parietal lobe covering the *supramarginal* and *postcentral gyri* (vwth = 2.24, $p = 0.006$, see **Figure 4.8**). For both figures below, average thickness changes was calculated after exclusion of the single outlier subject in the CCT group, as his rate of change was more than 2.5 SDs outside the group average. Note that this subject was not excluded in the above Freesurfer vertex analysis.

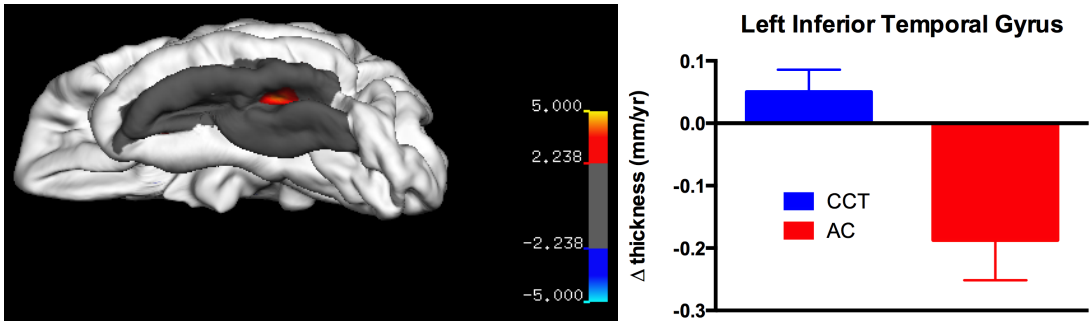


Figure 4.7: Vertex-based analysis of the left inferior temporal gyrus.

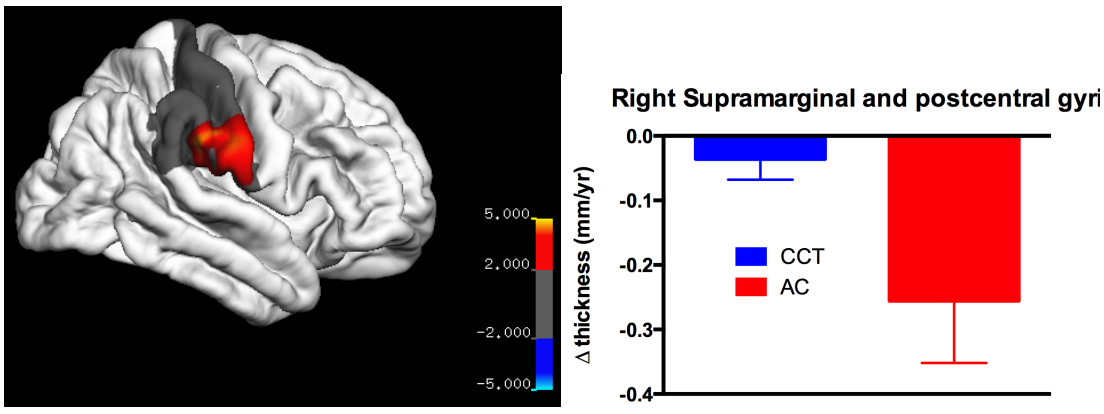


Figure 4.8: Vertex-based analysis of the right supramarginal and postcental gyri.

Resting-state fMRI. Compared to baseline, FC between the posterior cingulate and the superior frontal gyrus decreased in the CCT group and increased in the AC group at FU1 (group x time $p<0.01$). A statistically significant inverse correlation was found between the FC at FU1 and change in GC at FU2 ($r=-.602$, $p=0.038$), but only a trend towards significance was noted between the two deltas at FU1 ($r= -.530$, $p=0.076$, see **Figure 4.9**. No group differences were noted for FC change between the two regions at FU2.

Conversely, FC between the right hippocampus and the superior temporal gyrus increased in the CCT group and decreased in the AC group at FU1 (group x time $p<0.01$). A statistically significant correlation was found between FC and GC changes at FU1 ($r=.603$, $p=0.038$), and a trend towards significance was noted between FC change at FU1 and GC change at FU2 ($r= .533$, $p=0.074$, see **Figure 4.10**). No group differences were noted for FC between the two regions at FU2.

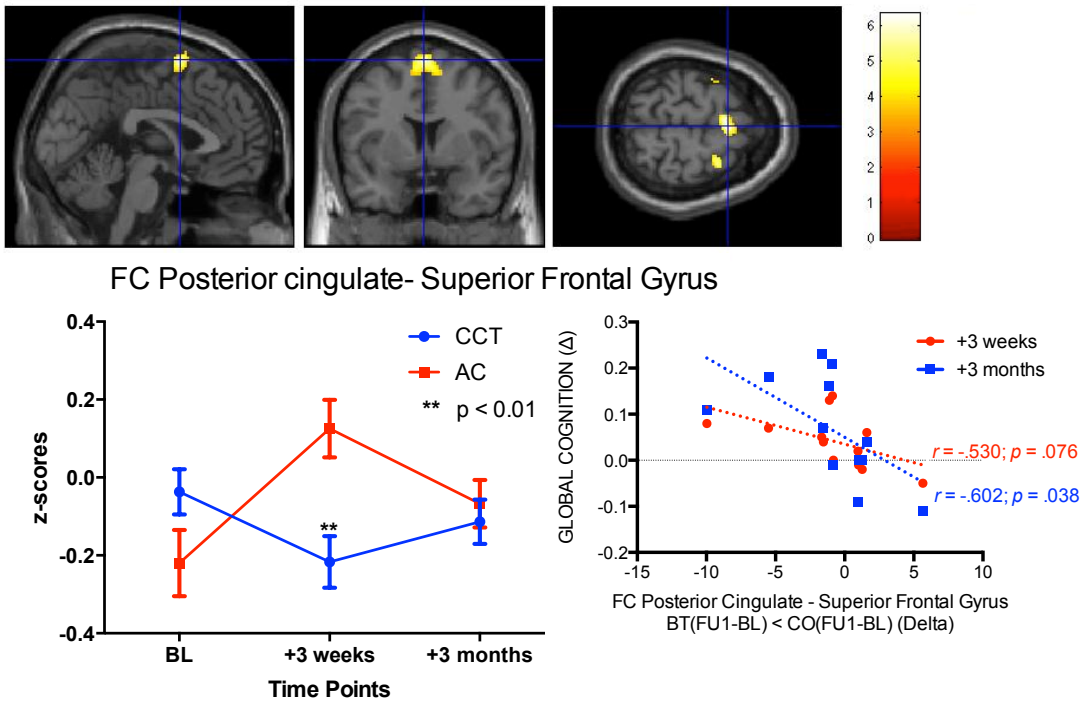


Figure 4.9: FC changes between the posterior cingulate and superior frontal gyrus at FU1 (+3weeks) and correlations with GC change at the same timepoint (+3 weeks) and at a delayed timepoint (+3months).

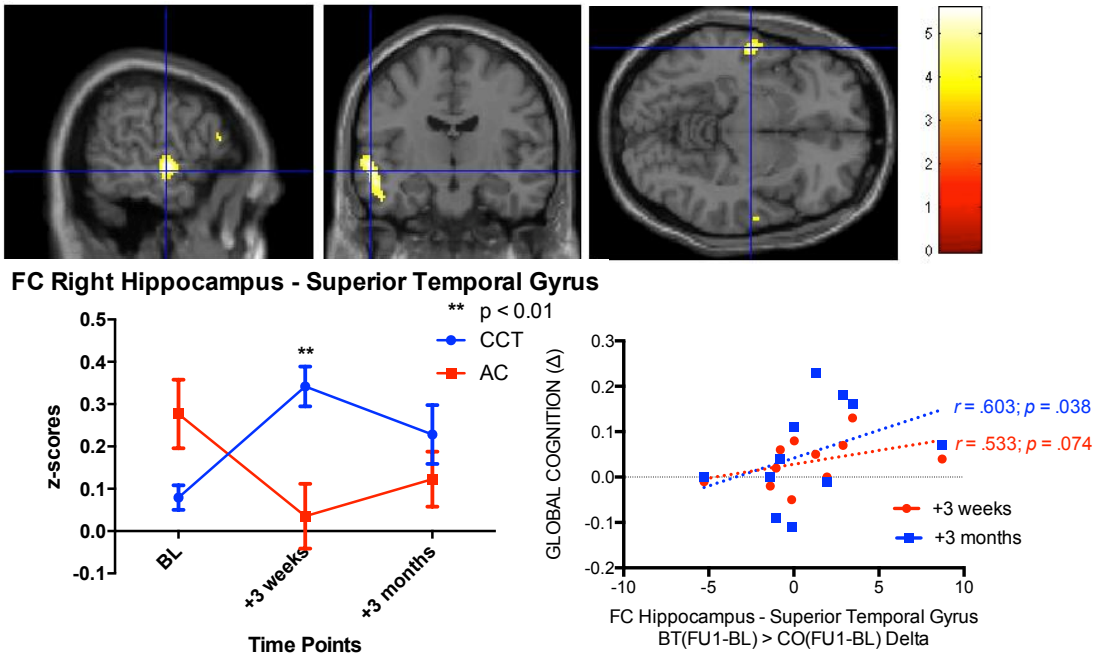


Figure 4.10: FC changes between the right hippocampus and superior temporal gyrus and correlations with GC change at FU1 and 2

No significant group x time interactions were found for any of the MRS data (see **Table 4.1**) or DTI analyses (data not shown).

		Posterior Cingulate					Hippocampus				
		CCT		AC		p-value	CCT		AC		p-value
		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
N-acetylaspartate/Cr	Baseline	2.23	0.16	2.24	0.28		1.74	0.06	1.84	0.06	
	Follow-up 1	2.14	0.07	2.25	0.29		1.74	0.11	1.72	0.05	
	Follow-up 2	2.30	0.24	2.26	0.28	0.36	1.72	0.15	1.74	0.15	0.32
Cholines/Cr	Baseline	0.45	0.07	0.44	0.10		1.06	0.05	1.12	0.10	
	Follow-up 1	0.43	0.03	0.46	0.12		1.09	0.05	1.13	0.17	
	Follow-up 2	0.42	0.03	0.45	0.11	0.45	1.07	0.11	1.17	0.11	0.49
Myo-inositol/Cr	Baseline	1.01	0.14	1.11	0.18		1.34	0.11	1.42	0.17	
	Follow-up 1	1.02	0.13	1.07	0.15		1.34	0.08	1.43	0.23	
	Follow-up 2	0.98	0.11	1.11	0.20	0.10	1.33	0.09	1.48	0.20	0.42
Glutamate+Glutamine/Cr	Baseline	0.33	0.07	0.21	0.15		0.88	0.19	0.87	0.27	
	Follow-up 1	0.24	0.08	0.16	0.13		0.88	0.11	0.75	0.17	
	Follow-up 2	0.23	0.07	0.15	0.12	0.82	0.89	0.17	0.90	0.18	0.20

Table 4.1: Metabolite values (normalized to Creatine) at the three time points. No significant time x group interactions were found. P-values refer to time x group effect.

4.4 Discussion

CCT effects on cortical thickness in the right postcentral gyrus were observed in a whole-brain VBM analysis (net effect size [NES]=1.48) and corroborated by the more biologically plausible Freesurfer-based cortical thickness analysis (NES=1.18). The postcentral gyrus is among the most age-sensitive cortical regions in terms of both volume[23-25] and function[26], and it is therefore possible that CCT attenuated the high rate of volume loss seen in that region in the control group. Moreover, volume change extracted from the VBM analysis correlated with positive change in global cognition, further suggesting a possible mechanistic explanation for CCT effects.

By contrast, between-group structural differences were noted over time in clusters around the fusiform and inferior temporal gyri, but the two analytical methods localised these to opposite hemispheres (NES=1.43). These findings are in line with previous studies in healthy older adults reporting structural[10] and functional CT-induced plasticity[12] in these specific segments of the ventral visual cortex, whose function also tends to change bilaterally with increasing age[27]. The effect of CCT could be therefore bilateral as well, albeit not robust enough to survive correction.

Training-induced differences on posterior cingulate–superior frontal gyrus functional connectivity (FC) and the hippocampus–superior temporal gyrus FC occurred early in the course of training (between baseline and FU1), but were not apparent nine weeks later. FC changes were therefore both temporally and spatially different from structural changes, suggesting that the two types of imaging can quantify distinct neuroplastic mechanisms. Importantly, however, both types of FC changes preceded subsequent structural change, and predicted subsequent cognitive change, and may so

serve not only as a possible mechanismtic explanation for CCT effect, but also as an early biomarker for titration of CCT. Clearly, given the small scale of this pilot study these findings will need replication in a larger study before their significance can be properly evaluated.

Lack of any significant time x group interactions on measures of FA and MRS are surprising, as CT-induced effects on these measures have been documented previously in healthy elderly. It should be noted, however, that the three studies reporting effects on FA[11,15,28] and the one study reporting effects on brain metabolites[8] had substantially larger sample sizes than here. Moreover, none of these studies included an active control group, and only one (non-randomised) study[15] used multidomain training. Multidomain training is likely to lead to more spatially distributed brain changes than repeated practice on essentially identical tasks over an long extended period.

Overall, the effects sizes generated from the imaging outcomes are higher than the GC gains in the overall Timecourse Trial (NES=0.49), but importantly, lower than the GC effect size in the imaging subsample (NES=2.18). The utility of neuroimaging as a CCT endpoint compared to cognitive endpoints is therefore doubtful[5]. Replication of these effect size estimates is critical, especially in a fully randomised design. Subjects in the current study were randomised only at the level of the whole trial, their entry into the imaging substudy influenced by a number of convenience factors. Arguably, the most useful outcome of this CCT imaging pilot study is therefore the ability to design future larger scale studies with some confidence.

Neuroimaging investigations of CCT may be useful for developing mechanistic explanations for training-induced cognitive effects, optimising training programs and

predicting response. Since functional outcomes were found to be more sensitive to short-term change, they may be more useful than sMRI as predictor of cognitive benefits.

This pilot investigation indeed suggests some intriguing insights into training-induced structural and functional plasticity that may explain and complement cognitive effects. However, this was a capital- and labour-intensive project, whose costs were similar to those spent on two-year Timecourse Trial. Hence, the extent to which the potential benefits from neuroimaging investigations of CT outweigh their costs remains unclear.

In conclusion, neuroimaging can provide a unique opportunity for understanding the neurobiological underpinnings of CCT[2], further development of effective interventions for specific neural impairments[4], and perhaps as a biomarker for clinical response. Further research is required to validate and extend upon these interesting preliminary findings.

References

1. Jaeggi SM, Buschkuehl M, Jonides J, Shah P. Short- and long-term benefits of cognitive training. *Proc Natl Acad Sci USA*. 2011;108(25):10081–10086. doi:10.1073/pnas.1103228108.

2. Suo C, Valenzuela MJ. Neuroimaging Outcomes of Brain Training Trials. In: Bright P, ed. *Neuroimaging - Cognitive and Clinical Neuroscience*. New York: InTech; 2012:417–430.

3. Belleville S, Bherer L. Biomarkers of Cognitive Training Effects in Aging. *Curr Transl Geriatr Exp Gerontol Rep*. 2012;1(2):104–110. doi:10.1007/s13670-012-0014-5.

4. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*. 2012;37(1):43–76. doi:10.1038/npp.2011.251.

5. Valenzuela M, Bartrés-Faz D, Beg F, et al. Neuroimaging as endpoints in clinical trials: are we there yet? Perspective from the first Provence workshop. *Molecular psychiatry*. November 2011:1064–1066.

6. Valenzuela MJ, Breakspear M, Sachdev P. Complex mental activity and the aging brain: molecular, cellular and cortical network mechanisms. *Brain Res Rev*. 2007;56(1):198–213. doi:10.1016/j.brainresrev.2007.07.007.

7. Coburn KL, Lauterbach EC, Boutros NN, Black KJ, Arciniegas DB, Coffey CE. The value of quantitative electroencephalography in clinical psychiatry: a report by the Committee on Research of the American Neuropsychiatric Association. *J Neuropsychiatry Clin Neurosci*. 2006;18(4):460–500. doi:10.1176/appi.neuropsych.18.4.460.

8. Valenzuela MJ, Jones M, Wen W, et al. Memory training alters hippocampal neurochemistry in healthy elderly. *Neuroreport*. 2003;14(10):1333–1337. doi:10.1097/01.wnr.0000077548.91466.05.

9. Lövdén M, Schaefer S, Noack H, et al. Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiol Aging*. 2012;33(3):620.e9–620.e22. doi:10.1016/j.neurobiolaging.2011.02.013.

10. Engvig A, Fjell AM, Westlye LT, et al. Effects of memory training on cortical thickness in the elderly. *Neuroimage*. 2010;52(4):1667–1676. doi:10.1016/j.neuroimage.2010.05.041.

11. Chapman SB, Aslan S, Spence JS, et al. Neural Mechanisms of Brain Plasticity with Complex Cognitive Training in Healthy Seniors. *Cereb Cortex*. 2013. doi:10.1093/cercor/bht234.

12. Brehmer Y, Rieckmann A, Bellander M, Westerberg H, Fischer H, Bäckman L.

Neural correlates of training-related working-memory gains in old age. *Neuroimage*. 2011;58(4):1110–1120. doi:10.1016/j.neuroimage.2011.06.079.

13. Mozolic JL, Hayasaka S, Laurienti PJ. A cognitive training intervention increases resting cerebral blood flow in healthy older adults. *Front Hum Neurosci*. 2010;4:16. doi:10.3389/neuro.09.016.2010.

14. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. *Neurobiol Aging*. 2007;28(2):272–283. doi:10.1016/j.neurobiolaging.2005.12.012.

15. Lövdén M, Bodammer NC, Kühn S, et al. Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*. 2010;48(13):3878–3883. doi:10.1016/j.neuropsychologia.2010.08.026.

16. Berry AS, Zanto TP, Clapp WC, et al. The influence of perceptual training on working memory in older adults. *PLoS ONE*. 2010;5(7):e11537. doi:10.1371/journal.pone.0011537.

17. Anguera JA, Boccanfuso J, Rintoul JL, et al. Video game training enhances cognitive control in older adults. *Nature*. 2013;501(7465):97–101. doi:Letter.

18. Suo C, León I, Brodaty H, et al. Supervisory experience at work is linked to low rate of hippocampal atrophy in late life. *Neuroimage*. 2012;63(3):1542–1551. doi:10.1016/j.neuroimage.2012.08.015.

19. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. *Neuroimage*. 2012;61(4):1402–1418. doi:10.1016/j.neuroimage.2012.02.084.

20. Ross AJ, Sachdev PS, Wen W, Valenzuela MJ, Brodaty H. 1H MRS in stroke patients with and without cognitive impairment. *Neurobiol Aging*. 2005;26(6):873–882. doi:10.1016/j.neurobiolaging.2004.07.008.

21. Ross AJ, Sachdev PS, Wen W, Valenzuela MJ, Brodaty H. Cognitive correlates of 1H MRS measures in the healthy elderly brain. *Brain Res Bull*. 2005;66(1):9–16. doi:10.1016/j.brainresbull.2005.01.015.

22. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*. 2006;31(4):1487–1505. doi:10.1016/j.neuroimage.2006.02.024.

23. Giorgio A, Santelli L, Tomassini V, et al. Age-related changes in grey and white matter structure throughout adulthood. *Neuroimage*. 2010;51(3):943–951. doi:10.1016/j.neuroimage.2010.03.004.

24. Li S, Xia M, Pu F, et al. Age-related changes in the surface morphology of the central sulcus. *Neuroimage*. 2011;58(2):381–390. doi:10.1016/j.neuroimage.2011.06.041.

25. Su L, Wang L, Chen F, Shen H, Li B, Hu D. Sparse representation of brain aging: extracting covariance patterns from structural MRI. *PLoS ONE*.

2012;7(5):e36147. doi:10.1371/journal.pone.0036147.

26. Balsters JH, O'Connell RG, Galli A, et al. Changes in resting connectivity with age: a simultaneous electroencephalogram and functional magnetic resonance imaging investigation. *Neurobiol Aging*. 2013;34(9):2194–2207. doi:10.1016/j.neurobiolaging.2013.03.004.

27. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol*. 2009;60:173–196. doi:10.1146/annurev.psych.59.103006.093656.

28. Engvig A, Fjell AM, Westlye LT, et al. Memory training impacts short-term changes in aging white matter: a longitudinal diffusion tensor imaging study. *Hum Brain Mapp*. 2012;33(10):2390–2406. doi:10.1002/hbm.21370.

Chapter 5: General Discussion

I would like to see once, only once in my life, a research report that does not end with the words 'further research is urgently needed'

Dr. Gerhard Kocher ('Vorsicht, Medizin!')

Forty years since CT was suggested as a means to address cognitive ageing[1], and almost 30 years after the first computerised exercises were trialled[2], the field has yet to develop a coherent rationale that could serve as a basis for further research, development and clinical practice. Tackling this problem will require more than simply more studies and more data. As argued in this concluding chapter, meaningful progress in the field will require better ways to test, communicate and implement CCT programs. Based on the findings described in this thesis, this chapter proposes a critical analysis of the current state of the field, and sets forth recommendations to strengthen CCT research and ensure its applicability.

5.1 Summary of Findings

Chapter 2 is to the best of the candidate's knowledge the most comprehensive systematic review of CCT in healthy older adults so far. It employed strict inclusion criteria, most notably randomised controlled designs and computerised interventions, and synthesised data from 37 eligible RCTs with 4,310 participants. By means of comparison, a recent Cochrane review covering the ill-defined area of 'cognition-based interventions' in healthy elderly *and* MCI[3] found a highly mixed set of 36 RCTs with 2,229 participants. A similar systematic review incorporating randomised along with nonrandomised trials of cognitive interventions in healthy elderly and

MCI[4] found 35 studies with 2,930 participants, and Kueider et al's[5] systematic review of CCT reported data from 38 studies with 3,205 participants, once more combining data from RCT with nonrandomised trials and including studies of computer-assisted cognitive stimulation along with CCT.

The findings reported in **Chapter 2** are therefore highly specific and up-to-date. They can be summarised in five key points. First and foremost, CCT produces small but statistically significant effect sizes on measures of memory, working memory, attention and visuospatial performance in this age group, as well as medium effect sizes on processing speed and language. The latter language effects are discounted because of a clear moderating effect of poor study quality. Second, no evidence for efficacy on any measure of executive functions was observed. Third, heterogeneity across studies was substantial, but is more likely to be explained by specific elements of intervention design factors than by a lack of active control groups, publication bias or study quality (except for language outcomes). Four, training programs that incorporate single-domain training, short sessions (<30 min), and more than three sessions per week were generally ineffective. Finally, effects on computerised, untrained neuropsychological measures was sometimes larger than on paper-based tests, and vice versa, depending on the cognitive domain.

Further support to these meta-analytical findings were provided in the Timecourse Trial in **Chapter 3**. This is the first RCT to show that centre-based multidomain CCT is effective on global cognition (GC), arguably the most relevant deficit in ARCD, along with efficacy on composite scores of memory and processing speed, measured primarily with computerised neuropsychological assessments. Compared to a rigorous active control condition, healthy older adults who received the CCT program showed

surprisingly rapid improvements in GC and processing speed, whereas memory gains followed a rather linear dose-responsive curve. Follow-up assessments three weeks post training revealed a rapid decay in GC and memory gains, whereas processing speed remained mainly constant. Two additional follow assessments at 3 and 12 months post-training showed a continuing moderate decay of gains, but residual effects were still noted one year after training cessation. A small effect size (NES=0.20) was noted on ADL one year post training, but the trial was not sufficiently powered to test statistical significance on this outcome.

Chapter 4 discusses a pilot study in which a subset of participants from the Timcourse Trial (seven from the CCT group and five controls) underwent multimodal MRI scans at baseline, then after three weeks and three months of training. We aimed to examine the potential of neuroimaging to provide mechanistic explanations for CCT-induced cognitive gains, as well as to assess the putative role of neuroimaging outcomes as endpoints for CCT trials. Rigorous statistical analyses found CCT-induced volumetric benefits in two regions implicated in age-related atrophy (sensorimotor and ventral visual cortices), as well as positive correlations between volumetric changes in the postcentral gyrus and gains in global cognition. Further, we found a short-term change in functional connectivity between the posterior cingulate and the superior frontal gyrus, as well as between the right hippocampus and superior temporal gyrus. Both of these changes preceded structural changes and predicted later GC gains. On the other hand, as effect sizes were considerably smaller than those obtained from cognitive measures in the same sample, the value of imaging may stem mainly from revealing mechanistic changes rather than as biomarkers of intervention efficacy, at least as suggested by this modest preliminary investigations of multidomain CCT.

5.2 Limitations

The overall aim of this thesis was to address current barriers to wide-scale implementation of CCT in the healthy elderly, as well as to guide research priorities in the field. Consequently, the work had to be limited to a narrow band of questions and analyses, and did not carry out a large number of further analyses that could have been of theoretical interest as noted below. Similarly, generalisation of the findings to other populations and interventions may be limited.

In order to increase its relevance to the immediate field, the meta-analysis described in **Chapter 2** was limited to RCTs of strictly-defined CCT in healthy elderly. This decision led to the exclusion of a substantial pool of studies, such as otherwise methodologically robust non-randomised trials (e.g., the large COGITO trial[6]), and studies in MCI population, despite the difficulty to distinguish between MCI and normal ageing (see **Chapter 1**). Conversely, neuropsychological outcomes were not preselected but rather combined based on general cognitive constructs, and it is reasonable to assume that this design decision has decreased the precision of the estimated effect.

As discussed above, the Timecourse Trial (**Chapter 3**) used a cohort to examine two theoretically and methodologically distinct issues, namely the overall long- and short-term effects of CCT on GC on one hand, and the dose-responsiveness of GC and its components on the other. In order to achieve the latter aim, participants in the trial underwent essentially the same neuropsychological assessment six times over the course of 15 months. This method may have exacerbated test-retest effect in the sample, which arguably diminishes the probability of observing transfer from training into untrained tasks[7]. Yet, the fact that significant effects have been observed

repeatedly in the data strengthens the argument in favour of CCT efficacy rather than weakens it. That said, alternative explanations of theoretical importance such as order effect in the battery and the possibility that CCT induces resilience to cognitive fatigue rather than increases cognitive capacities[7], have not been examined in the current study and remain an open field for research.

Finally, the neuroimaging analyses conducted in a subsample of participants from the Timecourse Trial were most certainly limited by the small sample size, a disproportional number of CCT vs AC subjects, and gender imbalances between the two groups, all of which resulted from practical constraints beyond the control of the candidate (see **Chapter 4**). Thus, although andattempt was made to counterbalance these limitations with conservative analytical methods, the results of this pilot version must be examined with caution and warrant validation in larger samples.

5.3 Toward the Next Wave of CCT Trials

The studies conducted in this thesis were designed to address ongoing problems in the field of CCT in older adults. **Chapter 2** was an effort to shift the evidence base from a binary efficacy question (*'does it work?'*) to a critical evaluation of specific design features (*'what works?'*). **Chapter 3** provides a novel and concrete example of this type of trial, simultaneously addressing the effectiveness of CCT on GC (generalisation) and also the temporal dynamics of CCT in terms of dose-responsiveness and durability across domains. **Chapter 4** pushes the field even further by posing mechanistic questions (*'how does it work?'*), albeit in a preliminary form[8,9].

5.3.1 Increasing Outcome Relevance

Previous and ongoing CCT trials can be divided into two broad categories. Most have focused on simple efficacy questions, a considerably smaller proportion have considered moderator and mediator effects, and, in rare cases, conducted head-to-head comparisons of different CT programs. This effort has resulted in a plethora of data, but given the range of approaches, data synthesis has been a challenge and led to wildly divergent conclusions from systematic and non-systematic reviews. **Chapter 2** has to an extent helped address this issue by focusing on potential moderators of treatment efficacy in a quantitative manner.

Yet a more ambitious step towards establishing the ecological validity of CCT may require a rethinking of our definition of effectiveness. If the ultimate goal of CCT is to maintain elders' everyday function, reliable measures of the latter will need to be developed and implemented as primary outcomes[10]. At the same time, clear clinical outcome measures such as incident diagnosis, mobility and functional independence are needed to assess the effectiveness of CCT in primary and secondary prevention of dementia. Surrogate outcomes, even global cognition indices, may not provide the confidence in the intervention sought by clinicians and decision-makers. On the other hand, global and domain-specific cognitive outcomes may continue to be useful for more specific purposes such as restoration of specific cognitive impairments at the individual level and research about how to best maintain training-induced gains.

CCT trials are resource-intensive and require a considerable deal of effort on behalf of both researchers and participants. Such trials may therefore be difficult to fund, recruit and conduct, especially in community settings. Yet, large sample sizes will be essential to detection of functional efficacy in healthy elderly. For example, the effect

size of NES=0.20 on B-ADL will require a total sample size of N=800 to meet the α=0.05 with 0.8 power. The field cannot avoid these any more, as it is this kind of clinically- and community- relevant outcomes that changes practice (as witnessed in the cardiology field[11]). What is therefore missing is multicentre networks of like-minded clinical researchers in order to expedite and efficiently carry out large multicentre and even multinational trials. The enhanced definition of likely key moderators of CCT efficacy identified in **Chapter 2** is a positive contribution to the future design of such landmark trials.

5.3.2 Enhancing Cognitive Efficacy

Clearly, further work is required to develop evidence-based training protocols that are capable of producing durable effects on everyday cognitive health. Three major challenges arise: a tendency for gains to be domain-specific; adherence to demanding and time-consuming interventions over the long term; and the limited durability of training effects. Possible solutions based on the findings of **Chapters 2 and 3** will now be discussed in turn.

*Training program***.** A multidomain training program has the greatest likelihood of effectiveness. The program should include both visual and auditory modalities and balance training schedules to maintain constant challenge in every targeted domain. In principle, training programs should adapt content in difficulty to individual performance, based on predefined goals. Regardless of content, 2-3 training sessions lasting 30-60 minutes is recommended by the current findings.

*Settings***.** Similarly to physical training, the effect of CCT relies on a combination of factors such as choosing the appropriate exercises, adequate performance, feedback, reinforcement, perseverance and emotional satisfaction. Software has limited ability

to address all these factors, and is unable to deliver nonspecific factors such as socialisation, which are likely to further augment training sessions and are an inherent part of centre-based training (and controlled for in active control centre-based studies). Although the net contribution of these factors to training efficacy is largely unknown in healthy older adults, it may be possible to draft supervision guidelines based on methods from the cognitive rehabilitation literature. Moreover, researchers and clinicians with an interest in CCT should be taught how to build and supervise training sessions, moreover, with some form of certification and quality assurance in place. In most countries personal fitness instructors need some form of mandatory training and qualification (e.g., in Australia it involves a Certificate IV qualification with a minimal course duration of 515 hours); why cognitive fitness instructors do not require any minimum training can no longer be defended particularly given the level of community and commercial interest.

*Booster***.** Once a target improvement in cognitive performance has been reached (or more likely a ceiling level of improvement as seen in **Chapter 3**), further training will be needed in order to maintain the benefits in the long-term. This may be possible, for example, by using distant CCT systems that provide patients with training on their personal computers, allow trainers to follow-up on their patients' performance, and enable early detection of decay of cognitive gains that may trigger a face-to-face setting. Booster sessions have been found to maintain training benefits one year after training cessation, but effects depend on the specific training protocol and outcome measures used[12-14].

*Targeting executive and everyday functions***.** As discussed in **Chapter 2,** further work is needed in order to address the current inefficacy of CCT on executive function

outcomes. In addition, clinical CCT may adopt methods from the cognitive rehabilitation field, targeting specific individual deficits in everyday performance by providing training on specific everyday tasks. Such training may be based on immersive technologies, which are becoming increasingly affordable and expands the quality and variety of computerised rehabilitation techniques. For example, Optale et al[15] reported gains in several cognitive functions, including GC, in a sample of care facility residents following a virtual reality program that trained everyday memory tasks using a head-mounted display and joystick. Similarly, Grewe et al[16] developed 360^0 virtual supermarket environment, which involve touch screens, sound and motion, but has yet to be trialled in older adults.

5.3.3 Combining Cognitive and Imaging Data to Optimise Training

A synthesis of the dose-response data discussed in **Chapter 3** and **4** may suggest a new way for framing multidomain CCT based on the common medical ideas of '*loading dose'*, '*titration'* and '*maintenance dose*' (see **Figure 5.1**). Initially, we observed steep therapeutic response curves, characterized by large gains from relatively few training sessions, a period conceptualized as loading dose. These were complemented by changes in functional connectivity and a moderate structural response in the sensorimotor cortex. Thereafter, global gains continue to rise but follow a logarithmic function, where individuals will experience diminishing returns as they approach peak therapeutic response. Conversely, the rate of structural change has increased compared to the 3-week timepoint, suggesting that structural plasticity may follow an exponential function, and that cortical volumes could increase further if training would have been continued. Thus, peak-response finding procedure may be advantageous at this point (titration). Following the offset of training, therapeutic

gains decay quickly, but some residual effects on GC can persist for at least 3-months. It is during this time that booster training is indicated and forms the third maintenance phase. Currently, there is no biological understanding for how CCT cognitive gains decay – and this is a fertile area doe future research. Mechanistic and applied research in this field may benefit by clearly distinguishing between these three therapeutic phases.

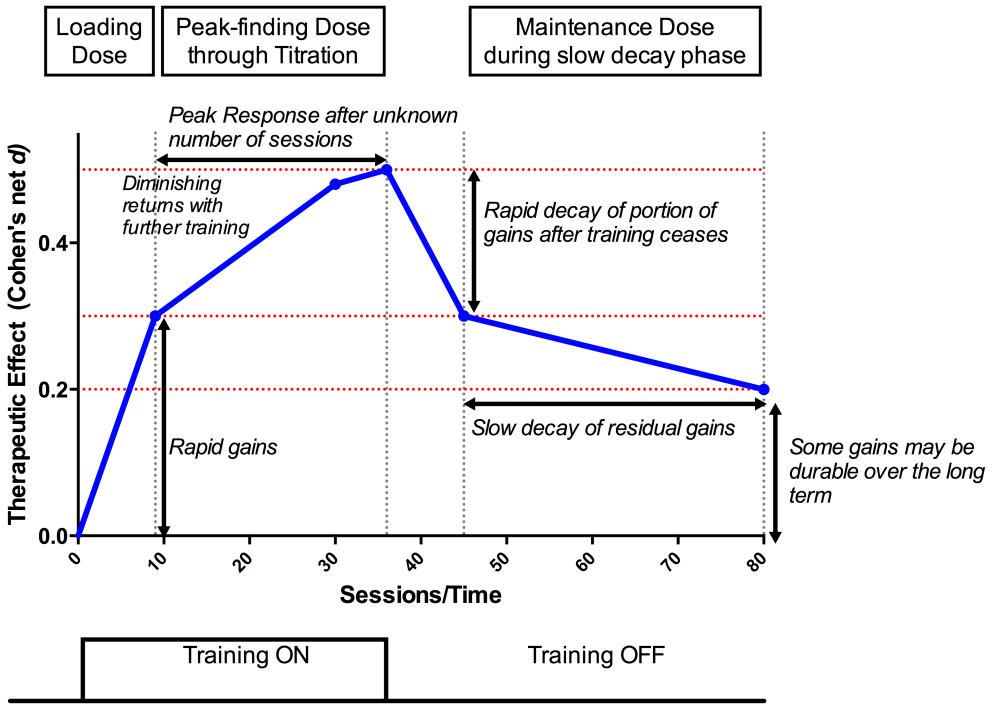


Figure 5.1: Therapeutic heuristic for multidomain supervised Computerized Cognitive Training in older individuals. Sessions refer to number of consecutive CCT sessions implemented three times a week, and time to the equivalent period after stopping training. Three main phases are distinguished: loading dose, during which rapid therapeutic effects may be seen; titration, during which the trainer identifies peak therapeutic response beyond which further training is inefficient; and maintenance, during which rapid decay of gains are lost but residual therapeutic effects may be conserved especially with use of booster sessions.

5.3.4 Improving Ethical and Reporting Standards

As scientific and commercial interest in CCT is growing, the impact of the current lack of standards or regulation is beginning to surface. Although **Chapter 2** did not find evidence of publication bias, a close examination reveals some potential issues that need to be addressed. More generally, some practices in an already polemical field are worrying and warrant a debate about establishing clear guidelines for research and communication.

*Inconsistent terminology and reporting standards***.** As discussed in **Chapter 1**, the terms used to describe cognitive interventions vary to nearly the same extent as the interventions themselves. Combined with the typically poorly detailed description of the interventions, it may be difficult to replicate previous studies and virtually impossible to implement them in clinical practice. This is a substantial and preventable waste of research efforts[17]. It is thus imperative to develop a consensus taxonomy for the field, encourage authors to follow them and provide full disclosure of critical elements in the CCT intervention, including, among others, public access to a training manual that details training protocols, supervision methods and software version.

*Conflict of interests***.** Of the 37 studies reviewed in **Chapter** 2, 24 (65%) used commercially available CCT programs or prototypes of commercial products. There is no doubt that CCT should be produced and sold in the marketplace like any other medical product or service, and that scientific investigation of these products is equally desirable (as done in **Chapter 3**). Yet, more than half of the studies using commercial products were co-authored by employees or financial stakeholders of the companies whose products were under investigation. Under these circumstances the

degree to which possible conflict of interest has affected reporting remains difficult to assess. Like in the wider debate about big-pharma sponsored research, full and open access to all primary data may be essential to ensuring confidence in commercial-CCT sponsored research.

*Clear communication of results to the public***.** Critics of the multi-million 'brain fitness industry' sometimes argue that commerce is getting ahead of science and that companies' claims of efficacy largely lack empirical evidence[18]. **Chapter 2** clearly shows that this argument is not correct for CCT as a whole, but does not neutralise the argument. Insofar as academic integrity is concerned, CCT researchers should not limit their role to simple academic conduct and reporting, but also to ensuring that research findings are not misused and championing higher standards for the field in general.

5.4 Conclusion

ARCD is a major concern for Australia's rapidly ageing population and an existential threat to the Australian economy. CCT is among the very few interventions that can improve cognitive performance in the elderly[19], and is therefore a candidate intervention for primary and secondary prevention.

The 'brain training debate' is therefore, hopefully, over. At the very least the conversation needs to change. This thesis makes a strong case for the efficacy of CCT on elders' cognitive performance. It also reveals a number of crucial design factors that underpin effective CCT, showed that these effects are dose-dependent, charted their short- and long-term dose response curves, and provided insights for how neuroimaging can be used to reveal potential underlying mechanisms. Beyond this,

this thesis is the first to show robust and durable CCT-induced gains on global cognition, hence taking the field towards its next challenge – establishing effectiveness on everyday function and ultimately as a possible means to better prevent dementia.

This thesis must therefore conclude with only a partial fulfilment of Dr Kocher's wish: that not more research is required but *different* research. The time has come to begin to establish consensus guidelines around CCT, impose training standards for the field, design large clinical trials that can deliver results of greater relevance, and disseminate these results in a useful and unambiguous manner. Novelty in the field will not stem from yet another medium-sized trial of a yet another CCT program, but rather by examining its clinical and societal relevance.

References

1. Hoyer WJ, Labouvie GV, Baltes PB. Modification of Response Speed Deficits and Intellectual Performance in the Elderly. *Human Development*. 1973;16(3):233–242.

2. Ball K, Sekuler R. Improving visual perception in older observers. *J Gerontol*. 1986;41(2):176–182.

3. Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database Syst Rev*. 2011;(1):CD006220. doi:10.1002/14651858.CD006220.pub2.

4. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: a systematic review. *Ageing Res Rev*. 2013;12(1):263–275. doi:10.1016/j.arr.2012.07.003.

5. Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: a systematic review. *PLoS ONE*. 2012;7(7):e40588. doi:10.1371/journal.pone.0040588.

6. Schmiedek F, Lövdén M, Lindenberger U. Hundred Days of Cognitive Training Enhance Broad Cognitive Abilities in Adulthood: Findings from the COGITO Study. *Front Aging Neurosci*. 2010;2. doi:10.3389/fnagi.2010.00027.

7. Green CS, Strobach T, Schubert T. On methodological standards in training and transfer experiments. *Psychol Res*. 2013. doi:10.1007/s00426-013-0535-3.

8. Belleville S, Bherer L. Biomarkers of Cognitive Training Effects in Aging. *Curr Transl Geriatr Exp Gerontol Rep*. 2012;1(2):104–110. doi:10.1007/s13670-012-0014-5.

9. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. *Neuropsychopharmacology*. 2012;37(1):43–76. doi:10.1038/npp.2011.251.

10. Zelinski EM. Far transfer in cognitive training of older adults. *Restor Neurol Neurosci*. 2009;27(5):455–471. doi:10.3233/RNN-2009-0495.

11. Valenzuela M, Esler M, Ritchie K, Brodaty H. Antihypertensives for combating dementia? A perspective on candidate molecular mechanisms and population-based prevention. *Transl Psychiatry*. 2012;2:e107. doi:10.1038/tp.2012.28.

12. Cheng Y, Wu W, Feng W, et al. The effects of multi-domain versus single-domain cognitive training in non-demented older people: a randomized controlled trial. *BMC Med*. 2012;10:30. doi:10.1186/1741-7015-10-30.

13. Ball K, Berch DB, Helmers KF, et al. Effects of cognitive training

interventions with older adults: a randomized controlled trial. *JAMA*. 2002;288(18):2271–2281.

14. Wolinsky FD, Vander Weg MW, Howren MB, Jones MP, Dotson MM. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults. *PLoS ONE*. 2013;8(5):e61624. doi:10.1371/journal.pone.0061624.

15. Optale G, Urgesi C, Busato V, et al. Controlling memory impairment in elderly adults using virtual reality memory training: a randomized controlled pilot study. *Neurorehabil Neural Repair*. 2010;24(4):348–357. doi:10.1177/1545968309353328.

16. Grewe P, Kohsik A, Flentge D, et al. Learning real-life cognitive abilities in a novel 360°-virtual reality supermarket: a neuropsychological study of healthy participants and patients with epilepsy. *J Neuroeng Rehabil*. 2013;10:42. doi:10.1186/1743-0003-10-42.

17. Hoffmann TC, Erueti C, Glasziou PP. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *BMJ*. 2013;347:f3755.

18. Chancellor B, Chatterjee A. Brain Branding: When Neuroscience and Commerce Collide. *AJOB Neuroscience*. 2013;2(4):18–27. doi:doi: 10.1080/21507740.2011.611123.

19. Hindin SB, Zelinski EM. Extended practice and aerobic exercise interventions benefit untrained cognitive outcomes in older adults: a meta-analysis. *J Am Geriatr Soc*. 2012;60(1):136–141. doi:10.1111/j.1532-5415.2011.03761.x.

Appendix 1: COGPACK Training Schedule

Session	Exercises used							
Session 1	Reading	UFOs	Color&Labels	New-or-Not	Logic	Anagrams		
Session 2	Route	Sequences	Scales	Comparisions	Compass	Mathematics		
Session 3	Sequence	Eyewitness	Archive	Ball	Search	Position		
Session 4	Reading	Sequences	New-or-Not	Connect	Clock	Labyrinths		
Session 5	Memory	Sequences	Route	Reaction	Follow-up	Color&Labels	Anagrams	Position
Session 6	Eyewitness	Scales	Comparisions	Compass	Archive	Numbers		
Session 7	Reading	Sequences	UFOs	Logic	Guess Words	Search	Position	
Session 8	Memory	Sequences	Connect	Clock	Route	Numbers		
Session 9	Eyewitness	Sequences	Color&Labels	Guess Words	Logic	Archive	Position	
Session 10	Sequence	New-or-Not	Scales	Comparisions	Compass	Mathematics		
Session 11	Memory	Route	Reaction	Logic	Search	Guess Words	Position	
Session 12	Eyewitness	Sequences	Archive	Connect	Labyrinths	Numbers		
Session 13	Reading	Sequences	New-or-Not	UFOs	Color&Labels	Guess Words	Position	
Session 14	Route	Sequences	Scales	Comparisions	Compass	Mathematics		
Session 15	Eyewitness	Sequences	Archive	Ball	Logic	Search	Position	
Session 16	Reading	Sequences	New-or-Not	Connect	Mathematics	Clock	Labirynths	
Session 17	Memory	Sequences	Route	Reaction	Logic	Guess Words	Position	
Session 18	Eyewitness	Sequences	Archive	Comparisions	Compass	Mathematics		
Session 19	Reading	UFOs	New-or-Not	Logic	Sequences	Search	Guess Words	Position
Session 20	Memory	Sequences	Connect	Clock	Labyrinths	Numbers		
Session 21	Sequence	Ball	Follow-up	Color&Labels	Archive	Concepts	Position	
Session 22	Piece-work	Wisdom	New-or-Not	Scales	Comparisions	Mathematics		
Session 23	Memory	Route	Sequence	Who-or-What	Clock	Position		
Session 24	Labyrinths	Eyewitness	Archive	Sequence	Numbers	Clock	Reaction	

Session 25	Wisdom	New-or-Not	Sequence	Logic	Color&Labels	Who-or-What	Position	
Session 26	Memory	Route	Scales	Comparisons	Compass			
Session 27	Eyewitness	Ball	Logic	Search	Sequences	Concepts	Archive	Position
Session 28	New-or-Not	Connect	Labyrinths	Numbers	Sequences	Logic		
Session 29	Wisdom	Archive	Sequence	UFOs	Search	Position		
Session 30	Eyewitness	Route	Sequence	Scales	Color&Labels	Compass		
Session 31	Memory	Sequences	Follow-up	Clock	Guess Words	Numbers	Position	
Session 32	Reading	New-or-Not	Sequence	Ball	Color&Labels	Labyrinths		
Session 33	Memory	Route	Sequence	Logic	Connect	Mathematics		
Session 34	Sequence	Who-or-What	Comparisions	Reaction	Archive	Search		
Session 35	Wisdom	New-or-Not	Compass	Scales	Mathematics	Logic	Position	
Session 36	Sequence	Reaction	Clock	Color&Labels	Concepts	Route		

Appendix 2: COGPACK Exercise Descriptions

Note: The descriptions below are based on exercise descriptions provided in COGPACK version8 help files. COGPACK is copyrighted by Marker Sofware, Landenburg, Germany.

Anagrams: A meaningful word must be made out of the letters provided. This exercise trains the use of meaningful linguistic material at word-level.

Archive: The trainee is given titles to pictures, and must then remember them either actively or passively.

Ball: The trainee must keep a ball bouncing using a horizontally movable paddle. This exercise trains visuomotor skills.

Clock: Set and read an analogue clock.

Color & Labels: *Task 1* - Colour labels are written in the colour they mean (e.g. word blue is written in blue), with one exception (e.g. word green is written in red). The wrong colour label must be clicked on. *Task 2* - A block of colours or patterns displays all but one of the selections shown in a multiple choice list. The missing one has to be found. *Task 3* - Short-term memory tasks with colours and labels.

Comparisons: Compare two simultaneously appearing character strings.

Compass: Recognize and enter compass points using on-screen compass

Concepts: Work out the concept/rule linking various terms. This exercise trains meaningful linguistic material at concept level.

Connect: Using mouse clicks, join up points according to given rules

Eyewitness: Trainees must recall short street scenes with random combinations of image, text, sound and movement elements. This exercise trains quick perception and passive reproduction of several simultaneous stimuli.

Follow-up: Continue a series of characters according to deducible rules.

Guess Words: Based on word length and definition, trainees must guess a word using the fewest number of letter clues. This exercise trains meaningful linguistic material at a relatively simple word-level.

Labyrinths: Using the mouse or cursor keys, trainees must sscape from randomly generated labyrinths which only have one solution and one exit.

Logic: *Task 1* –Formal comparison of abstract quantities. This exercise trains deductive thinking. *Task 2* – Complete a block of regularly ordered characters. Rule recognition. Like many intelligence tests. Task 3 – Logical "AND and OR" exercises. LOGIC "And and Or" is designed for learning some basic rules of logical combination.

Mathematics: Trainees must solve arithmetic problems, complex puzzles and problems using basic algebra and tasks which use everyday problems (percentages, sales tax).

Memory: Trainees are required to solve memory tasks using selectable material (e.g. text, graphics) and selectable recall options (e.g. immediate or delayed).

New-or-Not: Numerous items will be presented on the screen, and trainees must indicate if they have seen the item previously.

Numbers: Numerals expressed in roman, binary, hexadecimal form or in words from various languages must be entered in arabic-decimal numbers or vice versa

Piece-work: This is a simulation of an assembly line. Trainees must remove defective pieces.

Position: The position of 3-D bodies in space must be remembered or reproduced

Reaction: This exercise trains reaction rime, and requires trainees to respond to certain stimulus as quickly as possible according to given instructions

Reading: Trainees must memorize presented texts and then answer questions on it.

Route: Trainees must follow must note the route indicated on a map and then must reproduce this.

Scales: Scales must be brought into balance using as few as possible of the weights available.

Search: Trainees must search for a particular item hidden in a distracting background.

Sequence: A set of continuous performance tasks. Trainees must rapidly click on items based on their relationship to previous items according to a given rule.

UFOs: Use the mouse to catch UFOs flying in from random directions. This exercise trains hand-eye coordination.

Who-or-What: *Task 1* - The description of a person or a concept is given either letter by letter or as running letters. As soon as the item has been guessed, the stop button must be pressed and the answer entered. *Task 2* - Trainees must match labels to pictures.

Wisdom: Trainees must memorize quotes and the individuals who said them.