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Cochrane Database of Systematic Reviews 2018, Issue 7. Art. No.: CD013069.
DOI: 10.1002/14651858.CD013069.

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[Intervention Protocol]

Cognitive training for people with mild to moderate dementia

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New, published in Issue 7, 2018.

Citation: Bahar-Fuchs A, Martyr A, Goh AMY, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. *Cochrane Database of Systematic Reviews* 2018, Issue 7. Art. No.: CD013069. DOI: 10.1002/14651858.CD013069.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

- To evaluate the effects of cognitive training on cognitive and non-cognitive outcomes for people with mild to moderate dementia and their caregivers.
- To compare the effects of cognitive training with those of other non-pharmacological interventions, including cognitive stimulation or rehabilitation.
- To identify and explore factors related to intervention and trial design that may be associated with the efficacy of cognitive training.

BACKGROUND

Description of the condition

Dementia is a clinical syndrome in which functional independence is compromised due to intellectual and cognitive impairment (mostly of gradual onset). It is typically caused by age-related pathophysiological processes. Alzheimer's disease (AD) and mixed AD and cerebrovascular disease are the most common causes of dementia in older people (Alzheimer's Association 2018). Other common causes include Lewy-body pathology (in dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)) and frontotemporal lobar degeneration (in the frontotemporal dementias (FTD), and there are numerous other, rarer causes) (Alzheimer's Disease International 2009).

Dementia due to most neurodegenerative conditions is usually associated with aggregates of folded or misfolded proteins (Villemagne 2018). In the case of dementia due to AD, this includes aggregates of the Aβ protein that form into plaques in the space between neurons, as well as aggregates of misfolded tau protein that form neurofibrillary tangles inside neurons. Other protein-aggregates are implicated in other neurodegenerative disease (e.g. TDP-43 in FTD, alpha-synuclein protein aggregates in dementia with Lewy bodies). Aggregated proteinopathies usually spread in a predictable and well-described manner through cortical and subcortical regions (Braak & Braak 2012). In the case of most dementia aetiologies, the pathophysiological chain of events

commences years or even decades before the onset of obvious clinical symptoms, at which stage individuals are increasingly brought to clinical attention (Alzheimer's Association 2018).

Regardless of cause, dementia usually has an insidious onset and progressive course (although in some cases, e.g. vascular cognitive impairment, a more rapid onset may be seen) (Wilson 2012). While the clinical presentation in the early or mild stages may vary according to the underlying disease aetiology, global cognitive impairment, changes in personality and behaviour, and compromised functional independence are common characteristics with clinical progression. Cognitive impairment (in the case of AD and vascular disease) and behavioural, personality, or language changes (in the case of frontotemporal neurodegeneration) are typically present well before a clinical diagnosis is made, but in the early stages these can be difficult to differentiate from common age-related changes or from symptoms associated with common psychiatric conditions (e.g. depression), a factor that often leads to delays in bringing the situation to medical attention. During the pre-dementia phase, individuals usually present with mild cognitive impairment (Albert 2011; Petersen 2004), a period in which cognitive impairment can be detected on formal examination, but there is usually no, or only minimal, impairment in the ability of the individual to carry out most activities of daily living. In the mild to moderate stages of dementia, cognitive impairment becomes more profound and widespread, functional disability becomes increasingly evident - particularly in relation to more complex activities - and caregiver burden tends to significantly increase (Berger 2005; Gaugler 2000). In the more advanced stages of dementia, most cognitive and functional abilities are profoundly impaired, and behavioural changes such as apathy, depression, aggression and agitation are frequently observed (Förstl 1999).

Despite some overlap, the cognitive symptom signature that characterises the different disease aetiologies that tend to develop into dementia can often be distinguished, at least in the early stages. In the case of dementia due to AD, the earliest cognitive signs on formal neuropsychological examination are almost invariably related to episodic memory function. Within the memory domain, the most striking deficits are usually observed on measures of new learning and delayed recall, deficits which precede the diagnosis of AD by several years (Weintraub 2012). Once deficits on measures of learning and memory have developed, individuals often show increasing difficulty performing tasks related to semantic memory, language, executive functions, and visuospatial/constructional abilities. In dementia with Lewy bodies, early cognitive impairments are more likely to involve striking visuospatial deficits, fluctuating attention and reduced working memory capacity, and the development of vivid hallucinations. In dementias related to frontotemporal lobar degeneration, early symptoms may be predominantly behavioural and related to social cognition in behavioural-variant FTD, or involve predominantly language skills and verbal expression in the temporal subtypes (Weintraub 2012). Although impaired performance on measures of episodic memory is also central to vascular dementia, people with this condition typically display a more striking deficit on executive and attention tasks, as well as on measures of semantic knowledge and visuospatial function (Graham 2004).

Dementia is highly prevalent in older people, is a leading cause of disability worldwide, and is associated with enormous financial, emotional, and societal burden (Wimo 2017), making research in this area a global priority (World Health Organization 2012). Despite years of research and numerous clinical trials, no cure is yet available for any of the irreversible causes of dementia. Cholinesterase inhibitors remain the primary pharmacological treatment for the cognitive symptoms in AD and related dementias; however, the effects of these drugs are not universal and are always temporary (Birks 2006). A range of non-pharmacological interventions (NPIs) that target different aspects of the clinical syndrome, associated disability and caregiver burden are available (for a comprehensive systematic review, see Olazaran 2010). NPIs are generally not disease-specific and do not directly engage underlying biological targets, and are therefore not 'disease-modifying'. On the other hand, NPIs are more likely to target a broader spectrum of clinically meaningful outcomes, and are less likely to cause adverse reactions. Within the broad category of NPIs, cognition-oriented treatments, and particularly cognitive training, have been the subject of much interest among researchers, clinicians, and the general public.

Description of the intervention

"Cognition-oriented treatments" (COTs), referred to previously as "cognition-focused interventions" (Clare 2002; Clare 2004), is an umbrella term referring to a group of NPIs in which a range of techniques are applied in order to engage thinking and cognition with various degrees of breadth and specificity. Unlike NPIs that are primarily oriented toward outcomes which are behavioural (e.g. wandering), emotional (e.g. anxiety) or physical (e.g. sedentary lifestyle), in COTs the goals include improving or maintaining cognitive processes or addressing the impact of impairment in cognitive processes on associated functional ability in daily life (Bahar-Fuchs 2013; Clare 2004). Cognitive training (CT), sometimes described in the literature as 'brain training', 'retraining' or 'remediation') typically involves guided practice of a set of structured - and usually standardised - tasks, designed to train relatively well-defined cognitive processes and abilities such as speed of information processing, attention, memory, or problem-solving (Bahar-Fuchs 2013; Mowszowski 2010). Other COTs described in the literature include cognitive stimulation therapy (CST), and cognitive rehabilitation (CR), and these approaches are regarded as distinct in terms of their underlying theoretical assumptions, core elements, and the contexts or populations in which they have been traditionally applied, but it is acknowledged that some overlap exists and that differentiating between these approaches is not always straightforward (Bahar-Fuchs 2013; Gates 2014). Indeed,

these terms have been and continue to be applied somewhat interchangeably in the literature (e.g. Fernandez-Prado 2012; Giordano 2010), despite the availability of broad definitions and descriptions of these distinct forms of intervention (Bahar-Fuchs 2013; Clare 2004; Woods 2012). Table 1, below, summarises key defining features and common properties of these approaches. Cognitive stimulation is the focus of a separate Cochrane Review, which concluded that general cognitive stimulation consistently produces improvements in general cognition and, in some cases, in self-reported quality of life and well-being, primarily for people with mild to moderate dementia (Woods 2012). Cognitive rehabilitation, which is an inherently individualised approach emphasising collaborative goal-setting and a functional orientation (Bahar-Fuchs 2016; Clare 2001), has been considered alongside CT in previous versions of this Cochrane Review (Bahar-Fuchs 2013; Clare 2004); however, as the body of evidence for this approach has increased in recent years, and as it involves different methods and targets different outcomes, it will be considered in a separate Cochrane Review and the current review will accordingly focus only on CT.

Cognitive training

Cognitive training is historically couched within the broader field of neuropsychological rehabilitation of individuals with brain injury and neurological diseases, with efforts to systematically retrain specific cognitive functions originally described by clinical researchers such as Leonard Diller and Yehuda Ben-Yishay in their pioneering work with victims of stroke and head trauma throughout the 1970s (Ben-Yishay 1978; Diller 1974). In the early 1980s, the principles of CT began to be applied in cognitively healthy older adults with subjective cognitive complaints (e.g. Zarit, 1981), however it was not until the late 1980s that cognitive training was first attempted with people with dementia (e.g. Beck 1988). A central assumption underlying cognitive training is that practice has the potential to improve or at least maintain functioning in the given cognitive domain. A further important assumption is that any effects of practice will generalise beyond the immediate training context. In other words, improved performance on a given task should lead to improved performance on other, related tasks that depend on the same cognitive process or ability. Although this last assumption has not often been supported by the evidence (Owen 2010; Papp 2009), some have argued that failure to produce transferable benefits is related in part to problems with task design (Jaeggi 2010). As noted above, CT traditionally involves the repeated practice of a set of structured tasks designed to target particular cognitive processes and abilities. Some authors have proposed that cognitive training should be divided into subtypes of cognitive exercise, and strategy training (Gates 2011), which involves instruction and practice in the use of specific cognitive strategies designed to further enhance performance, or minimise the impact of impaired cognition (e.g. method of loci, visual imagery) (Hampstead 2016). Cognitive training is different to the type of skill training often exercised by occupational therapists in that the target is usually an underlying process or ability, rather than a specific skill. While early versions of CT tended to be delivered in an inflexible 'one size fits all' approach, technological developments are leading to increasing tailoring of training focus based on individual cognitive profile and adaptive difficulty level in recent years (Bahar-Fuchs 2017; Peretz 2011). Cognitive training may be offered through individual sessions (Davis 2001; de Vreese 1998a; de Vreese 1998b Farina 2002; Koltai 2001; Loewenstein 2004), or group sessions (Cahn-Weiner 2003; Ermini Fuenfsch 1995; Kesslak 1997; Koltai 2001; Moore 2001), or may be facilitated by family members with therapist support (Neely 2009; Quayhagen 1995a; Quayhagen 2000). Initially delivered mainly in paper-and-pencil formats, computerised cognitive training (CCT) programmes have largely replaced more traditional methods over the past two decades (Davis 2001; de Vreese 1998; Quayhagen 1995; Quayhagen 2000). In some cases, the tasks or activities which form the focus of practice/training are analogues of actual daily activities, such as doing online shopping or setting up a dinner table (Farina 2002; Loewenstein 2004; Neely 2009; Zanetti 1994; Zanetti 1997; Zanetti 2001), and in these cases the distinction between cognitive training and functional skills training becomes more difficult. Skills-oriented interventions in which the target task is well structured, broken into relatively well-defined underlying cognitive performance elements, and where the outcomes of interest are cognitive processes rather than merely the performance of the intervention task itself (e.g. Neely 2009), appear to fit the conceptual framework of cognitive training. Conversely, where the focus of the intervention is a specific skill and there is no expectation to improve an underlying cognitive ability/process, and where the cognitive underpinnings are unclear or only vaguely addressed, the intervention might be best classified as 'functional skills training'. In accordance with the suggestion that cognitive training may enhance the effects of pharmacological therapy (Newhouse 1997), some studies have evaluated the efficacy of cognitive training in combination with the use of cholinesterase-inhibitors (Cahn-Weiner 2003;de Vreese 1998a; de Vreese 1998b Loewenstein 2004), or other medications (Heiss 1993; Yesavage 1981).

Table 1. Selected characteristics of cognitive training, stimulation, and rehabilitation			
	Cognitive training	**Cognitive rehabilitation**	**Cognitive stimulation**
Target	Impairment	Participation restriction	Participation restriction
Context	Structured tasks and environments	In the person's natural environment	Usually in a clinic/residential care, or daycare setting
Focus of intervention	Specific cognitive abilities and processes. Psychoeducation and strategy training sometimes included	Groups of cognitive abilities and processes required to perform individually-relevant everyday tasks. Behaviour, environment and everyday activity. Psychoeducation and strategy training sometimes included	Orientation, Global cognitive status
Format	Individualised or group	Individualised	Typically group
Proposed mechanism of action	Mainly restorative; mechanisms related to neuroplasticity	A combination of restorative and compensatory approaches; reduction of 'excess disability'	Improved orientation, general activation
Goals	Improved or maintained ability in specific cognitive domains	Performance and functioning in relation to collaboratively set behavioural or functional goals	Improve overall orientation and engagement in pleasant abilities

How the intervention might work

Cognitive training aims to improve or maintain specific cognitive processes or global cognitive ability, and when used as an intervention approach with clinical populations, there is also an expectation that improvements in cognition will generalise to improvements in functional outcomes. Much has been written about the lack of unifying theories in the field of NPIs, including in relation to interventions aimed at changing behaviour (Michie 2008), cognition and function (Wilson 2002), and in relation to rehabilitation in general (Hart 2014). Indeed, no single theory exists that comprehensively explains such issues as why or how cognitive training should lead to improved cognitive and functional outcomes, whether and why some cognitive domains are more likely to respond to training than others, whether training should target single or multiple cognitive domains, or whether it should focus on improving impaired functions or building on preserved ones. To various extents, cognitive training interventions in healthy and in clinical populations draw instead on a range of theories and discoveries grounded in cognitive neuroscience (e.g. Jaeggi 2008; Sohlberg 1987), clinical practice and rehabilitation of patients with neurological injuries and diseases (Stuss 1999; Ponsford 2012), and continues to be shaped in response to relevant technological developments including in the gaming industry (Anguera 2015). Unfortunately, many cognitive training interventions have been and continue to be developed without clear reference to any relevant theoretical work.

A central assumption held by many advocates of cognitive training is that training an underlying cognitive ability or process will lead to generalised improvements that go beyond the training context (Lampit 2014). In cognitively healthy younger and older adults, and to a lesser extent, in individuals with mild cognitive impairment (MCI), there is little doubt that CT leads to improvements on trained or 'criterion' tasks. However, in both healthy and clinical populations, the evidence concerning learning transfer remains mixed, and the issue is hotly debated, with much of the debate concerning the identification of barriers and enablers of transfer of gains to untrained tasks that reflect the cognitive domain tar-

geted by the training (near transfer) and other untrained cognitive domains as well as non-cognitive outcomes (far transfer) (Jaeggi 2010). In a recent comprehensive review and critique of the commercial cognitive training industry, Simons and colleagues point out that the discussion concerning transfer of learning can be traced back to very early theoretical accounts (Simons 2016), such as the so-called formal discipline theory, and the theory of transfer by identical elements proposed by Edward Thorndike in the early 20th century. It is beyond the scope of this review to cover these in detail, but a critical discussion of these accounts in relation to the cognitive training literature and industry is included in the review by Simons and colleagues (Simons 2016). Contemporary empirical findings suggest that factors that appear to be implicated in cognitive training-related gain-transfer include the degree of similarity or overlap in elements of trained and transfer tasks, extent of actual gain on trained tasks, baseline cognitive abilities, and age (Zinke 2014).

In addition to theories of learning and transfer, knowledge and expertise related to brain-behaviour relationships - as well as of mechanisms of injury, disease and recovery - are critical in informing the development of COTs, including cognitive training, in the context of work with persons with acquired disorders of the central nervous system (including traumatic brain injury, stroke and neurodegenerative conditions). Historically, such interventions have reflected two broad conceptual frameworks for the recovery of function after brain illness or injury: a restorative approach, and a contextualised or compensatory approach (Ylvisaker 2002). Techniques usually associated with cognitive rehabilitation, such as optimising residual cognitive abilities in impaired domains and making the most of unimpaired cognitive abilities, lend themselves more to compensatory approaches (Clare 2001b). In contrast, techniques usually associated with CT, such as the repeated exercise of standardised cognitive tests of increasing difficulty, and the targeting of specific cognitive domains, tend to reflect restorative principles and "thrive on the lure of neuroplasticity" (Rabipour & Raz 2012). Indeed, a range of neuroplasticity-related observations in animal and human studies, including changes at the molecular, synaptic, structural, and functional level associated with enriched environments and a structured training programme, are routinely cited as the proposed mechanisms of action in cognitive training (Valenzuela 2012). In recent years, growing evidence has shown that cognitive training is associated with changes in patterns of neural activation in key brain regions in healthy older adults (Belleville 2014), and in people with MCI (Belleville 2011; Hampstead 2011). Such increased brain activation may be the result of processes of synaptic growth and repair triggered by repeated practice on standardised tests.

Why it is important to do this review

The Alzheimer's disease drug development pipeline is slow and trials of disease modifying treatments have generally failed to produce improvements in any clinically-meaningful outcomes, despite succeeding in disrupting targeted pathophysiological processes (Cummings 2014; Cummings 2016; Salomone 2012), leading some to question the relevance of the dominant amyloid cascade hypothesis when it comes to the development of an effective treatment for dementia as a clinical syndrome (D'Alton 2011). NPIs aimed at developing ways for living better with dementia, in part by targeting relevant clinical outcomes and caregiver burden, are assuming an increasingly central role in the management of dementia and are recognised as an important adjunct, and even alternative, to available pharmacological treatments. A recent Lancet Commission on Dementia Prevention, Intervention, and Care argues that some NPIs can already play an important role in managing some of the cognitive, behavioural and neuropsychiatric symptoms of dementia, and points to the positive findings for cognitive stimulation therapy and the preliminary supportive evidence on cognitive rehabilitation (Livingston 2017).

In healthy older adults (Edwards 2017; Lampit 2014), and in persons with MCI (Chandler 2016; Hill 2017), systematic review findings on the effects of cognitive training on cognitive and several non-cognitive outcomes have been generally encouraging, and factors associated with increased intervention efficacy in CT are becoming better understood. Indeed, in recently published clinical practice guidelines for MCI, cognitive training has been classified as having Level C evidence, meaning that clinicians may recommend this form of intervention (Petersen 2018).

In contrast, most systematic reviews of CT for persons with dementia have to date produced largely negative findings (e.g. Bahar-Fuchs 2013; Hill 2017; but see Sitzer 2006). Our previous Cochrane Review of CT for persons with dementia included 11 randomised controlled trials, but there was no evidence to support CT in relation to any of the examined outcomes. We noted, however, that the certainty of these findings may be reduced by the relatively small number of highly heterogenous studies, which were often of low methodological quality. Against the background of a heavily divided scientific community, and an ever growing industry of commercial CT products that have at times made highly misleading claims, it is vital that clinicians, policy-makers, and the general public are presented with up-to-date, rigorous and unbiased review of the current literature on cognitive training for persons with mild to moderate dementia.

OBJECTIVES

- To evaluate the effects of cognitive training on cognitive and non-cognitive outcomes for people with mild to moderate dementia and their caregivers.
- To compare the effects of cognitive training with those of other non-pharmacological interventions, including cognitive stimulation or rehabilitation.

- To identify and explore factors related to intervention and trial design that may be associated with the efficacy of cognitive training.

METHODS

Criteria for considering studies for this review

Types of studies

In keeping with previous version of this review, and to ensure the inclusion of unbiased estimates of treatment effects only (Reeves 2011), we will only consider randomised controlled trials (RCTs) for inclusion. Wherever possible, we will not exclude studies published in a language other than English, and we will make every effort to obtain an English translation from the authors. In cases where a translation cannot be obtained from the authors, we will engage in reasonable efforts to obtain a reliable translation, and will only exclude a study if these efforts are unsuccessful.

Types of participants

We will include participants with a medical diagnosis of all-cause dementia or of any specified subtype of dementia as long as the underlying aetiology was assumed to be non-reversible. The diagnosis of dementia should be made on the basis of established clinical or research diagnostic criteria, including criteria specified by the following.

- The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V, APA 2013) or earlier versions (APA 1995)
- The International Classification of Diseases, Tenth Revision (ICD-10) (WHO 1992)
- The National Institute of Neurological and

Communicative Disorders - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann 1984)

- The National Institute of Health-Alzheimer's Association (NIA-AA) (McKhann 2011)
- The Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) (Roman 1993).
- Vascular Impairment of Cognition Classification Consensus Study (McKeith 1996; McKeith 2006; McKeith 2017)
- The International Behavioural Variant FTD Criteria Consortium (FTDC) (Skrobot 2017)

On average, participants in included studies will be classified as being in the mild to moderate level of severity. Dementia severity will usually be determined in primary trials on the basis of group mean scores, ranges of scores or individual scores on a standardised scale such as scores of over 12 at the Mini-Mental State Examination (MMSE; Folstein 1975) or scores of 0.5 to 2 on the Clinical Dementia Rating (CDR 2; Hughes 1982).

- Studies in which it is clear that only small proportion of participants (i.e. fewer than 15%) falls within the more severe range or the questionable dementia range will be considered acceptable if this information is clearly indicated in the study.
- Qualifying participants will generally be residing at home, or in a residential care facility. We will exclude studies in which recruited participants could be long-term residents of psychiatric hospitals, where pre-existing psychiatric conditions are likely to be present.
- We will set no specific age restrictions, although it is expected that, with the exception of participants with younger onset dementia (YOD), most participants will be 65 years of age and older.
- No restrictions will be placed on current pharmacological treatment. Where available, information about participants' use of cholinesterase inhibitors will be noted.
- Primary studies which include a mixture of participants, only some of whom meet our inclusion criteria (e.g. dementia and MCI), are eligible for inclusion as long as outcomes are reported separately for the group of interest.

Types of interventions

Experimental interventions

Interventions meeting our definition of cognitive training (CT) are eligible for inclusion. As the terms used to refer to CT vary considerably, interventions may be referred to as 'brain' or 'mental' training and they may be described as 'retraining', 'exercise', 'stimulation', 'rehabilitation', 'therapy', 'remediation', 'support', etc. Our operational definition of eligible interventions includes the following criteria.

- Participants are trained on tasks designed to target one or more cognitive processes either directly or indirectly. Training generally takes the form of repeated practice. Trials in which the primary goal was to compare performances of participants who learned how to perform a task under different learning conditions (e.g. errorless versus errorful) in a single session (single trial training) are not eligible for inclusion.
- Tasks may be completed in pen-and-paper format or through computerised exercises, or may be structured analogues of everyday tasks in which the cognitive underpinnings are explicit, and the intervention targets a cognitive ability or process rather than a specific skill. The nature of the intervention (i.e. computerised or pen-and-paper or analogues of daily activities) will be noted.
- Interventions may be delivered on commercially-available platforms, or be designed specifically for the purposes of the study.

- Interventions can target single or multiple cognitive domains.
- Level of difficulty is expected to vary, however this will not form part of the inclusion criteria.
- We will exclude from this review interventions in which cognitive training was combined with another distinct experimental intervention (e.g. physical activity, brain stimulation), but this does not apply to standard treatments as participants are generally expected to remain on their standard (usually pharmacological) treatment.
- Modified/alternative cognitive training: it is acknowledged that CT and other cognition-oriented treatment approaches (i.e. cognitive stimulation or rehabilitation) may share some features, and are not always straightforward to distinguish between. Hence, we will include trials of complex cognition-oriented treatments that also include elements of cognitive stimulation (e.g. orientation), rehabilitation (e.g. goal setting), or psychoeducation (e.g. using cognitive strategies) if it is determined by consensus that CT is clearly the predominant component. Where relevant and indicated by statistical heterogeneity, we will consider these interventions separately in subgroup analyses.

Comparator interventions

- Wait-list. In studies of this kind, the experimental intervention is offered to the control group after the study had ended.
- No treatment/standard treatment. Unless otherwise specified, whenever groups are described as 'no treatment' in individual studies, we will assume that this refers to the usual/standard treatment, and not to withholding of treatment. 'Usual or standard treatment' refers to what would normally be provided in the study locality to participants with mild dementia, and might include provision of medication, clinic consultations, contact with a community mental health team, day care or support from voluntary organisations, but not a specific cognitive training intervention.
- Active control. This refers to conditions in which participants engage in some form of activity, typically for an equivalent number of sessions or visits, and receive similar levels of contact with the researchers, but during which no structured intervention is offered.
- Alternative treatment. These are distinct, alternative treatments, either cognition-focused (e.g. cognitive stimulation), or not (e.g. physical activity).

All interventions

- We will include interventions conducted in individual or group format, with or without involvement of family caregivers.
- We will not impose restrictions regarding intervention dose-related parameters, including the overall duration of the intervention or the number of treatment sessions. However, as described above, we will exclude single-session treatments.

Types of outcome measures

We considered outcomes within the following broad categories as relevant for this review:

- clinical disease progression;
- cognitive outcomes;
- psychosocial outcomes for the person with dementia;
- psychosocial outcomes for the primary caregiver;
- surrogate/mechanism/biomarker outcomes;
- economic outcomes.

Although it is acknowledged that surrogate and economic outcomes are important, we determined them to be beyond the scope of the current review, and so the main primary and secondary outcomes will be selected from the top four categories, as further outlined below.

Primary outcomes

Outcomes for the person with dementia

- Global cognitive status at the end of treatment (i.e. immediately post-intervention). We will measure this by change in scores on screening measures of global cognition (e.g. MMSE, Montreal Cognitive Assessment (MoCa), and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)).
- Clinical disease severity in the short to medium term. We will measure this by change in scores on measures of clinical disease progression (e.g. CDR, DRS) in a follow-up assessment conducted between 3 and 12 months after treatment cessation.

Secondary outcomes

Outcomes for the person with dementia

- Global cognitive status in the short to medium term. We will measure this by change in scores on screening measures of global cognition (e.g. MMSE, MoCA, ADAS-Cog) at the relevant follow-up assessment.
- Domain-specific cognitive status at the end of treatment. We will measure this by change in scores on neuropsychological measures of: global cognitive composite scores, speed of processing, immediate memory, delayed memory, attention and working memory, language (naming), verbal letter fluency, verbal category fluency, and executive function.

- Domain-specific cognitive status in the short to medium term. We will measure this by change in scores on neuropsychological measures of: global cognitive composite scores, speed of processing, immediate memory, delayed memory, attention and working memory, language (naming), verbal letter fluency, verbal category fluency and executive function.
- Meta-cognition (self-reported) at the end of treatment, and in the short to medium term.
- Meta-cognition (informant-reported) at the end of treatment, and in the short to medium term.
- Mood (as reflected in change in self- or informant-reported measures of depression, anxiety, etc.) at the end of treatment and in the short to medium term.
- Capacity for activities of daily living, at the end of treatment and in the short to medium term.
- Behavioural and psychological symptoms of dementia (BPSD) at the end of treatment and in the short to medium term.
- General health or quality of life at the end of treatment and in the short to medium term.
- Participant burden as reflected in rates of retention of trial participants at the end of treatment.

Outcomes for the primary caregiver at the end of treatment

- Mood and well-being (as reflected in change in self reported measures of depression, anxiety, etc.) at the end of treatment and in the short to medium term)
- Burden of care at the end of treatment and in the short to medium term.
- Quality of life at the end of treatment and in the short to medium term.

Outcome measures

Where possible, we will use data from published and validated tests, questionnaires or techniques for the evaluation of a given outcome. In cases in which an outcome is evaluated by an unpublished or non-established measure, we will make every effort to source information about the statistical properties of the test or scale in question, before determining whether or not to accept the measure. We will classify the cognitive measures to specific cognitive domains according to established authoritative texts (Spreen 1998), wherever possible, and by consensus between the study authors as required.

Outcome evaluation

We will include trials if they include, at minimum, a baseline evaluation, and one post-treatment evaluation.

Search methods for identification of studies

Electronic searches

We will search ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group's (CDCIG) specialised register.

ALOIS is maintained by the Information Specialists for the Cochrane Dementia and Cognitive Improvement Group, and contains studies that fall within the areas of dementia prevention, dementia treatment and management, and cognitive enhancement in healthy elderly populations. The studies are identified through:

1. searching a number of major healthcare databases: MEDLINE, Embase, CINAHL and PsycINFO;
2. searching a number of trial registers: ClinicalTrials.gov and the World Health Organization's International Clinical Trials Register Platform (ICTRP) which covers ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others;
3. searching the Cochrane Library's Central Register of Controlled Trials (CENTRAL);
4. searching grey literature sources: ISI Web of Science Core Collection.

To view a list of all sources searched for ALOIS, please visit the ALOIS website (www.medicine.ox.ac.uk/alois).

Details of the search strategies run in healthcare bibliographic databases, used for the retrieval of reports of dementia, cognitive improvement and cognitive enhancement trials, can be viewed on the Cochrane Dementia and Cognitive Improvement Group's website: http://dementia.cochrane.org/searches

We will run additional searches in MEDLINE, Embase, PsycINFO, Cinhal, LILACs, ClinicalTrials.gov and the WHO Portal/ICTRP to ensure that the searches for this review are as comprehensive and as up-to-date as possible. The search strategy that will be used for the retrieval of reports of trials from MEDLINE (via the Ovid SP platform) can be seen in Appendix 1.

Searching other resources

We will screen reference lists from included trials, as well as the reference lists of recent systematic reviews, and relevant recent guidelines.

We will contact experts in the field in order to obtain additional randomised trial reports not identified by the search.

Data collection and analysis

Selection of studies

One review author (AM) will review titles and abstracts from the complete de-duplicated list of search results, and we will split the records for an independent screening by two additional authors (ABF, AG), in order to identify all potentially relevant RCTs of cognitive training for people with dementia and to remove obviously irrelevant studies. Whenever there is doubt regarding the eligibility of a trial, we will select it for full review of the methods. Following the initial screening, we will apply the same approach for the evaluation of the full methods from shortlisted articles. We will identify and merge multiple reports from the same study, and contact study authors to clarify issues related to the eligibility of a trial for inclusion. We will settle discrepancies in the classification of trials through discussion between two review authors and ruling of a senior author who is a content area expert (LC). The study selection process will be unblinded.

Data extraction and management

A trained research assistant (JS) will extract data from study reports onto a standardised, structured data entry form under the supervision of the lead author (ABF), who will also independently extract data for variables requiring some judgement (e.g. intervention integrity/fidelity), and we will subsequently enter the data into Review Manager 5 software (Review Manager 5). We will seek additional information from study authors as appropriate. Data extracted from each trial will include detailed characteristics of the trials (e.g. settings, outcomes), design features (e.g. delivery format, blinding), participant characteristics (e.g. diagnoses, age, gender, education, medications), elements of the experimental and control interventions (e.g. intensity, frequency, duration, key intervention features). We will also extract information about additional variables of interest for the investigation of effect moderators, including registration status, sources of funding, conflict of interest, adherence and retention, type of control, whether intervention integrity/fidelity was addressed, and adverse events. For each outcome of interest, we will extract mean scores and standard deviations on relevant measures from all available evaluations.

Assessment of risk of bias in included studies

Pairs of review authors will independently conduct the assessment of risk of bias using Cochrane's 'Risk of bias' tool (Higgins 2011). We will resolve disagreements by discussion with a third reviewer who is a subject matter expert (LC). Consistent with the Cochrane 'Risk of bias' tool, we will assess bias in the following domains: sequence generation, allocation concealment, blinding of participants and investigators, incomplete outcome data and selective reporting of outcomes. We will rate studies as 'low risk', 'high risk' or 'unclear risk' in each of these domains.

Measures of treatment effect

We will generally calculate effect estimates in primary trials along with their 95% confidence intervals (CIs) using change-from-baseline scores. Calculations of the standard deviation of change scores will make the assumption that the correlation between measurements at baseline and those at subsequent time points is r = 0.8, in keeping with other relevant reviews (e.g. Lampit 2014). However, for consistency with previous versions of this review, we will also conduct sensitivity analyses of the primary outcome with a conservative r = 0 assumption which overestimates the standard deviation of the change. We will treat outcome measures as measured on a continuous scale. In some cases, outcomes will be derived from ordinal rating scales; provided these contain a reasonably large number of categories (more than 10), we will treat data as continuous variables arising from a normal distribution. For dichotomous outcomes (e.g. participant retention), we will express effects as the risk ratio (RR) along with 95% CIs.

Unit of analysis issues

We expect four types of unit of analysis issue: cross-over trial designs, multiple-armed trials (more than one treatment/control condition), repeated assessments, and the availability of multiple measures of the same outcome in primary trials. Our approach to the management of these issues will be as follows.

- Cross-over trials: we will only use data from the first treatment period (before crossover).
- Multiple conditions
    - Experimental conditions: in trials that include at least three conditions, assuming that at least one condition satisfies our definition of a comparison condition (see above), we will combine data from all conditions that are judged to fit our definition of CT into a single group using relevant formula (Higgins 2011). We will exclude from this review trials that include two relevant experimental conditions but no eligible control condition.
    - Control conditions: we will combine data from two control conditions of the same broad type (i.e. no treatment). In the event that a trial includes different types of control comparisons which are not alternative treatments (e.g. it includes both no treatment and active control groups), we will use in the analysis data from both these control conditions by splitting the sample size of the experimental condition into two separate groups, following the procedure described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
- Repeated post-intervention assessments: we will conduct separate comparisons to assess the primary and secondary outcomes at the end of treatment (i.e. immediately post-intervention), and in the short to medium term (up to 12 months post-intervention). Within this follow-up period, we will use in the analysis data from the last available assessment We will

not use data from follow-up assessments conducted more than 12 months following the end of treatment assessment.

- Multiple measures of the same outcome: in primary trials in which multiple measures of the same outcome are used, the following principles will guide the selection of measures for data extraction.
  - General principles: we will use a composite outcome measure if one was derived by the authors. If no composite is available, we will generally use data from a test that matches the most commonly used measure in other studies that contributed data to the particular outcome. Established/published measures of the outcome will be preferred over measures developed for the specific study. If more than one established measure of an outcome was used, and no measure is identified that was used by the majority of trials contributing to the specific outcome, we will create a simple composite score from the standardised scores on the different measures and use it in the analysis.
  - Cognitive outcomes: for each trial, we will compute a global composite cognitive score by calculating a standardised change-from-baseline score from each measure (change score divided by the standard deviation of the change score), and deriving a simple mean and standard deviation of the Z scores associated with all cognitive measures from a trial. In addition, for the evaluation of domain-specific cognitive scores, we will use the following principles:
    - Psychomotor information processing speed. We will prefer visuospatial measures where available
    - Attention, immediate and delayed memory. We will prefer auditory-verbal measures for the evaluation of attention, immediate and delayed memory. We will prefer tasks that involve the learning of information over several trials (i.e. word lists) over tasks in which the information is only presented once (e.g. story or figure recall). We will prefer measures of free recall over measures of cued/recognition where available.
    - Executive functions. We will prefer tasks that reflect planning, organisation, decision-making, regulation of performance and set-shifting aspects of executive functions over tasks that are more strongly associated with volition or purposive action aspects of executive functions (Lezak 2004). In the event that several measures of executive function were used in a study, we will compute a composite executive function score by taking the mean of the standardised scores for each of these measures.
  - For meta cognitive outcomes, we will generally prefer self-reported measures of contentment/satisfaction with one's cognitive ability over informant-reported measures.
  - Mood outcomes: we will generally prefer measures of depression over measures of anxiety or apathy, and self-reported measures over informant-reported measures.
  - Activities of daily living (ADL): we will prefer measures of instrumental ADLs over measures of basic ADLs, and informant-reported measures over self-reported measures. This is based on the finding that self- and informant-reported daily function show significant discrepancy in people with dementia, and that informant reports of daily function are more closely associated with actual memory performance (Farias 2005).

Dealing with missing data

We will extract the number of participants who commenced and completed the intervention in each condition, and this will contribute to the assessment of risk of bias due to incomplete outcome data. Wherever possible, we will contact trial authors in an effort to obtain relevant unreported data. In general, we will assume that data are missing at random, and analyses in individual studies are generally performed on a per protocol (PP) rather than on an intention-to-treat basis (ITT). When a trial report includes relevant data from both the ITT and PP samples, we will generally use the PP data for consistency with most of the trials. We will evaluate the impact of missing data on pooled effect estimates in sensitivity analyses (see below).

Assessment of heterogeneity

In addition to a visual inspection of the forest plots, we will assess statistical heterogeneity using a standard Chi^2 statistic and the associated I^2 statistic. Consistent with recommendations (Deeks 2017), we will deem heterogeneity to be present when the Chi^2 statistic is significant at the $P = 0.1$ level, or when the I^2 suggests that more than 40% of the variability in effect estimate is due to heterogeneity. Where substantial heterogeneity is detected, we will explore the sources of heterogeneity through subgroup analyses (see below).

Assessment of reporting biases

For the primary outcomes, we will first evaluate the presence of reporting bias through a visual examination of funnel plots for small study effects. We will examine the significance of any apparent asymmetry with Egger's Test (Egger 1997), and follow up with the 'trim and fill' test (Duval 2000), if asymmetry of the plot is confirmed.

Data synthesis

We will perform data synthesis using Review Manager 5 software. In relation to each of the main outcomes of interest, we plan to undertake the following separate comparisons.

1. Cognitive training versus control (no/standard treatment/ wait list or active control) at the end of the treatment (i.e. immediately post-intervention).
2. Cognitive training versus control (no/standard treatment/ wait list or active control) in the short to medium term (3 to 12 months following end of treatment).

3. Cognitive training versus alternative treatment at the end of the treatment (i.e. immediately post-intervention).

4. Cognitive training versus alternative treatment in the short to medium term (3 to 12 months following end of treatment).

Within each of the planned comparisons, we will pool data in relation to each outcome of interest when data from at least two trials are available.

We will perform inverse-variance, random-effects meta-analyses for all outcomes. We will use the mean difference (MD) with 95% CIs whenever studies used the same outcome measure, whereas we will use the standardised mean difference (SMD), which is the absolute mean difference divided by the pooled standard deviation, when the same outcome is assessed by different measures.

In relation to the primary outcomes, we will express the overall quality and confidence in the evidence using GRADE levels and present this in 'Summary of findings' tables.

GRADE and 'Summary of findings' tables

We will describe the quality of evidence as 'high', 'moderate', 'low' or 'very low', using the GRADE framework, which we will apply to all primary and secondary outcomes in each of the comparisons. We will generate 'Summary of findings' tables using GRADEpro GDT software (GRADEpro GDT) and import these into the review. The 'Summary of findings' tables will include the following primary and secondary outcomes.

- Global cognition at the end of the intervention
- Clinical disease severity at the latest follow-up, up to 12 months following treatment cessation
- Delayed memory ability at the end of the intervention
- Capacity to perform activities of daily living
- Mood and well-being (participant)
- Mood and well-being (informant/caregiver)
- Treatment burden (retention rates)

Subgroup analysis and investigation of heterogeneity

In relation to each outcome, we will carry out subgroup analyses to evaluate the potential impact of categorical treatment modifiers. We will only carry out subgroup analyses where statistical heterogeneity is suggested by the relevant statistics (I^2 of 40% or more) (Deeks 2017), and assuming that at least three studies are available for each subgroup. We will examine the following categorical effect modifiers.

- Type of intervention 1: CT versus CT combined with elements of cognitive rehabilitation or cognitive stimulation (or both).
- Type of intervention 2: multidomain CT versus single domain (e.g. working memory).
- Intervention dose: more intense (i.e. more than three formal sessions per week) versus less intense interventions (i.e. up to three formal sessions per week).
- Intervention duration: longer interventions (i.e. more than three months) versus shorter interventions (i.e. three months or less).
- Follow-up period: we will compare studies with follow-up in the short term (up to three months after treatment cessation) with trials that included longer term follow-up (up to 12 months after treatment cessation).
- Risk of bias: studies with high risk of bias in at least two critical domains versus other studies with lower risk of bias. For the purposes of these analyses, critical domains are sequence generation, blinding of outcome assessment, incomplete data, and selective reporting. Although we acknowledge that allocation concealment is also increasingly regarded as a critical domain, this remains a relatively infrequent practice in these types of studies.
- Funding source: trials funded by commercial entities versus those based on competitive funding.
- Registration: registration status of the trial (prospective, retrospective, not-registered/not reported).

Sensitivity analysis

To determine whether findings for the primary outcomes are affected by assumptions made regarding the strength of the correlation between scores before and following the interventions, we will repeat the analyses of the primary outcomes after applying the zero correlation assumption, which overestimates the standard deviation of change scores. We will repeat the evaluation of the primary outcomes by a further sensitivity analysis using post-intervention scores only, thus avoiding the need to estimate the standard deviation of change scores.

ACKNOWLEDGEMENTS

For the current version

For previous versions:

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Dementia/
2 Delirium, Dementia, Amnestic, Cognitive Disorders/
3 dement*.mp.
4 alzheimer*.mp.
5 (lewy* adj2 bod*).mp.
6 (chronic adj2 cerebrovascular).mp.
7 ("organic brain disease" or "organic brain syndrome").mp.
8 (cerebr* adj2 deteriorat*).mp.
9 (cerebral* adj2 insufficient*).mp.
10 (pick* adj2 disease).mp.
11 PDD.mp.
12 "Parkinson* disease dementia".mp.
13 or/1-12
14 *Cognitive Therapy/
15 Rehabilitation Nursing/
16 Cognitive Remediation/
17 (cognit* adj2 stimulation).ti,ab.
18 (cognit* adj2 rehabilitation).ti,ab.
19 (cognit* adj2 training).ti,ab.
20 (cognit* adj2 retrain*).ti,ab.
21 "cognitive intervention*".ti,ab.
22 "Cognitive skills ADJ2 training".ti,ab.
23 "cognitive support".ti,ab.
24 "Cog* retrain*".ti,ab.
25 "memory function*".ti,ab.
26 (memory adj2 rehabilitation).ti,ab.
27 (memory adj2 therap*).ti,ab.
28 "memory aid*".ti,ab.
29 "memory group*".ti,ab.
30 "Memory rehabilitation".ti,ab.
31 "memory training".ti,ab.
32 "memory retraining".ti,ab.
33 "Memory rehabilitation".ti,ab.
34 "memory re-training".ti,ab.
35 "memory support".ti,ab.
36 "memory stimulation".ti,ab.
37 "memory strateg*".ti,ab.
38 "memory management".ti,ab.
39 or/14-38
40 randomized controlled trial.pt.
41 controlled clinical trial.pt.
42 randomized.ab.
43 placebo.ab.
44 randomly.ab.
45 trial.ab.
46 groups.ab.
47 or/40-46
48 (animals not (humans and animals)).sh.

49 47 not 48
50 13 and 39 and 49

CONTRIBUTIONS OF AUTHORS

Alex Bahar-Fuchs drafted the protocol. The previous version of the protocol (2001) served as a basis and was extensively modified as appropriate. All other review authors have read and commented on versions of the protocol.

DECLARATIONS OF INTEREST

Alex Bahar-Fuchs: none known

Anthony Martyr: none known

Anita MY Goh: none known

Linda Clare: none known

Julieta Sabates: none known

SOURCES OF SUPPORT

Internal sources

- Cochrane Incentive Award, UK.

External sources

- NIHR, UK.

This protocol was supported by the National Institute for Health Research (NIHR), via Cochrane Incentive funding Cochrane to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health

- National Health and Medical Research Council of Australia, Australia.