

Toward a theory-based specification of NON-PHARMACOLOGICAL treatments in aging and dementia:  
Focused reviews and methodological recommendations

Sietske A.M. Sikkes<sup>1#</sup>, Yi Tang<sup>4</sup>, Roos J. Jutten<sup>1</sup>, Linda M.P. Wesselman<sup>1</sup>, Lyn S. Turkstra<sup>5</sup>, Henry Brodaty<sup>6</sup>, Linda Clare<sup>7</sup>, Erin Cassidy-Eagle<sup>8</sup>, Kay L. Cox<sup>9</sup>, Gaël Chételat<sup>10</sup>, Sophie Dautricourt<sup>10</sup>, Klodian Dhana<sup>11</sup>, Hiroko Dodge<sup>12,13</sup>, Rose-Marie Dröes<sup>14</sup>, Benjamin M. Hampstead<sup>15</sup>, Thomas Holland<sup>11</sup>, Amit Lampit<sup>2</sup>, Kate Laver<sup>16</sup>, Antoine Lutz<sup>17</sup>, Nicola T. Lautenschlager<sup>2,18</sup>, Susan M. McCurry<sup>19</sup>, Franka J. M. Meiland<sup>14</sup>, Martha Clare Morris<sup>11</sup>, Kimberly D. Mueller<sup>20</sup>, Ruth Peters<sup>21,22</sup>, Gemma Ridel<sup>23</sup>, Aimee Spector<sup>24</sup>, Jenny T. van der Steen<sup>25,26</sup>, Jeanette Tamplin<sup>27</sup>, Zara Thompson<sup>27</sup>, on behalf of the ISTAART Non-pharmacological Interventions Professional Interest Area, Alex Bahar-Fuchs<sup>2,3#</sup>

**#Corresponding authors:** Sietske A.M. Sikkes, Amsterdam University Medical Centers, Alzheimer Center Amsterdam, PO Box 7057, 1007 MB, PK -1 Z 052, [s.sikkes@amsterdamumc.nl](mailto:s.sikkes@amsterdamumc.nl). Alex Bahar-Fuchs, University of Melbourne, [alex.bahar@unimelb.edu.au](mailto:alex.bahar@unimelb.edu.au)

**Affiliations**

<sup>1</sup> Alzheimer Center Amsterdam, Amsterdam University Medical Center, Amsterdam Neuroscience

VU University Amsterdam, Amsterdam, the Netherlands / VU University, Department of Clinical, Neuro- and Developmental Psychology, Amsterdam, the Netherlands

<sup>2</sup> Academic Unit for Psychiatry of Old Age, Department of Psychiatry, The University of Melbourne, Melbourne, Victoria, Australia

<sup>3</sup> Centre for Research on Ageing, Health, and Wellbeing, Research School of Population Health, The Australian National University

<sup>4</sup> Department of Neurology, Xuanwu Hospital, Capital Medical University, National Clinical Research Center for Geriatric Disorders, Beijing, China

<sup>5</sup> School of Rehabilitation Science, McMaster University, Hamilton, ON, Canada

<sup>6</sup> Centre for Healthy Brain Ageing and Dementia Centre for Research Collaboration, School of Psychiatry, UNSW Sydney, Australia

<sup>7</sup> Centre for Research in Ageing and Cognitive Health, College of Medicine and Health, University of Exeter, Exeter, UK

<sup>8</sup> Department of Psychiatry & Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA

<sup>9</sup> Medical School, University of Western Australia, Perth, Western Australia, Australia

<sup>10</sup> Normandie Univ, UNICAEN, INSERM, U1237, PhIND "Physiopathology and Imaging of Neurological Disorders", Institut Blood and Brain @ Caen-Normandie, Cycleron, 14000 Caen, France

<sup>11</sup> Section on Nutrition and Nutritional Epidemiology, Department of Internal Medicine, Rush University, Chicago, IL, USA

<sup>12</sup> Department of Neurology, Oregon Health & Science University, Portland, OR, USA

<sup>13</sup> Department of Neurology, University of Michigan, Ann Arbor, MI, USA

<sup>14</sup> Department of Psychiatry, Amsterdam University Medical Center, location VUmc, Amsterdam, the Netherlands

<sup>15</sup> Department of Psychiatry, University of Michigan & VA Ann Arbor Healthcare System, Ann Arbor, MI, USA

<sup>16</sup> Department of Rehabilitation, Aged and Extended Care, College of Medicine and Public Health, Flinders University, Adelaide, Australia

<sup>18</sup> Lyon Neuroscience Research Center INSERM U1028, CNRS UMR5292, Lyon University, Lyon, France.

<sup>18</sup> NorthWestern Mental Health, Melbourne Health, Melbourne, Australia

<sup>19</sup> Department of Child, Family, and Population Health Nursing, University of Washington, Seattle, WA, USA

<sup>20</sup> Wisconsin Alzheimer's Institute, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI, USA

<sup>21</sup> Department of Psychology, University of New South Wales, Randwick , Sydney, Australia

<sup>22</sup> Neuroscience Research Australia, 139 Barker Street, NSW 2031, Sydney, Australia

<sup>23</sup> The University of East Anglia, Norwich, UK

<sup>24</sup> Department of Clinical, Educational & Health Psychology, University College London, London, UK

<sup>25</sup> Department of Public Health and Primary Care, Leiden University Medical Center, Leiden, the Netherlands

<sup>26</sup> Department of Primary and Community Care, Radboud university medical center, Nijmegen, the Netherlands

<sup>27</sup> Faculty of Fine Arts and Music, The University of Melbourne, Victoria, Australia

**Conflict of interest statement:** GC reports coordination of a European Union Horizon 2020 program (Silver-Sante Study-Medit-Ageing). No stock options, patent or royalties. AL reports being co-investigator in clinical trials of computerized cognitive training using programs provided free-of-charge by HAPPYneuron Inc. and Synaptikon GmbH. GR and AS report offering training courses in CST and receiving occasional private income for training courses for dementia outside usual work. The remaining authors report no relevant conflict of interest.

**Funding statement:** ABF NHMRC Fellowship GNT1135605, SAMS JPND Zon-MW 733051043, RJ Zon-MW Memorabel 733050205, LW JPND Zon-MW 733051043, GC European Union Horizon 2020 program, Inserm, Fondation d'entreprise MMA des Entrepreneurs du Futur, Fondation Alzheimer,

This article is protected by copyright. All rights reserved.

Programme Hospitalier de Recherche Clinique, Région Normandie, Association France Alzheimer et maladies apparentées, Fondation Vaincre Alzheimer, RMD Association of Support VCVGZ for Chair Psychosocial care for people with dementia to stimulate further development, AL Partially funded by a grant from the German Federal Ministry of Education and Research (BMBF) for industry collaboration with Synaptikon GmbH in the field of cognitive assessment and training (ID 13GW0212A, 2017-2019). Received grants from the University of Melbourne and the Berlin University Alliance for development and piloting of systems for cognitive training personalisation and delivery of simultaneous cognitive and physical exercise (2019-2021); KL NHMRC-ARC Dementia Research Development Fellowship GNT1097435

<b>Article Type:</b>	Perspective Article
<b>Abstract word count:</b>	147
<b>Manuscript word count:</b>	6.723
<b>Tables:</b>	2
<b>Figures:</b>	4
<b>Supplemental files:</b>	2 (1 including Supplemental Text 1-14, 1 including Supplemental RTSS Tables 1 – 12)

## **Abstract**

**INTRODUCTION:** Non-pharmacological treatments (NPTs) have the potential to improve meaningful outcomes for older people at risk of, or living with dementia, but research often lacks methodological rigor and continues to produce mixed results.

**METHODS:** In the current position paper, experts in NPT research have specified treatment targets, aims and ingredients using an umbrella framework, the Rehabilitation Treatment Specification System.

**RESULTS:** Experts provided a snapshot and an authoritative summary of the evidence for different NPTs based on the best synthesis efforts, identified main gaps in knowledge and relevant barriers, and provided directions for future research. Experts in trial methodology provide best practice principles and recommendations for those working in this area, underscoring the importance of pre-specified protocols.

**DISCUSSION:** We conclude that the evidence strongly supports various NPTs in relation to their primary targets, and discuss opportunities and challenges associated with a unifying theoretical framework to guide future efforts in this area.

Author Manuscript

**KEYWORDS:**

Non-pharmacological, framework, mild cognitive impairment, subjective cognitive decline, neuropsychiatric, cognitive training, Cognitive Rehabilitation, Cognitive Stimulation Therapy, Nutritional interventions, Physical exercise training, Cognitive-Behavioral Therapy for Insomnia, Meditation, Reminiscence therapy, Music-based treatments, Communication treatments, Communication treatments, Multisensory treatments, Occupational therapy, Neuromodulation

Author Manuscript

## 1. Introduction

Dementia is currently one of the most pressing healthcare issues, with a worldwide rising prevalence due to the aging of the population and the absence of a curative therapy [1, 2]. The estimated global total costs of dementia were US\$ 818 billion in 2015, of which the majority was related to nursing home care and the informal care of caregivers. Dementia also has a considerable disease impact, affecting the quality of life of both people with dementia and their caregivers. Several diseases of the brain might underlie dementia, with Alzheimer's disease being the most common underlying cause.

Non-pharmacological treatments (NPTs) can be effective in the management of clinical symptoms and are likely to play an important role in the primary and secondary prevention of dementia. Advantages of NPTs are that they are generally well-accepted, have minimal adverse side-effects and can be combined with other NPTs both serially and simultaneously, and with pharmacological treatments without major concerns around interference. NPTs are also applicable to different clinical stages of disease, from dementia [3] to mild cognitive impairment [4] and even cognitively unimpaired adults at risk for dementia [5]. As such, NPTs have the potential of having a meaningful impact on cognition, well-being and quality of life throughout the course of age-related neurovascular diseases.

NPTs cover a diverse and broad range of intervention categories, including cognitive training, physical exercise, dietary treatments, art-oriented therapy and reminiscence therapy [6]. An influential previous meta-analysis defined NPTs as "any theoretically based, nonchemical, focused and replicable intervention, conducted with the patient or the caregiver, which potentially provided some relevant benefit" [7]. This and many other systematic reviews of NPTs in aging and dementia (e.g. [8]) have repeatedly pointed out the low quality of much of the evidence behind several NPTs. To improve the quality of evidence for NPTs, more coherent, targeted, and well-reported trials of higher methodological quality are needed, which will in turn lead to firmer conclusions regarding the extent and limits of gains associated with different types of NPT.

In 2015, the Non-Pharmacological Interventions Professional Interest Area (NPI-PIA) group was formed as a successor to the 'psychosocial understanding and intervention' PIA within the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment

(ISTAART). The NPI-PIA aims to address issues related to the design, methodology, and reporting of studies of NPT in the context of aging and dementia and to stimulate research in this area. In 2017, at the NPI-PIA Annual Meeting at the Alzheimer's Association International Conference (AAIC) in London, the Executive Committee and members agreed that there are several issues that affect progress in this broad field of research and deemed a position paper necessary. The main issues discussed included the need to a) identify and comment on key conceptual issues and challenges in response to rapid changes in thinking about dementia and underlying neurodegenerative diseases and their treatment, and b) advance a more coherent and theoretically-driven approach to the classification and description of NPI treatments, which would lead to c) improved methodological and reporting standards in this area of research.

In this paper, we offer a conceptual framework that may be useful for organizing and classifying research in NPT. We briefly summarize the body of work available in relation to key types of NPT in the context of people with dementia or at risk of dementia due to mild cognitive impairment, subjective cognitive decline or biomarker profiling, and identify key challenges. Finally, we provide methodological guidelines for the design of trials of NPTs, and conclude with several directions for future research.

## 1.1 Key conceptual issues

Here we briefly highlight some of the conceptual issues that were identified when considering and choosing the appropriate treatments and target groups for the current paper.

**Literature review:** We performed a search of the Cochrane Database of Systematic Reviews (September 2019), which yielded 122 systematic reviews on a variety of NPT categories, ranging from aroma therapy to vitamin D3 supplements. The majority of NPTs focused on persons with dementia. Figure 1 depicts the number of studies included in these Cochrane studies, with most



studies performed for Cognitive training and Chinese herbal medicine [8-10]. The quality grading for the level of evidence was modest at best.

[INSERT FIGURE 1]

**Target populations:** The current overview focuses on individuals with dementia and those in pre-dementia at risk stages. Treatments in which the target is someone other than the person with or at risk of cognitive decline (e.g., family members, caregivers, GPs, etc.), and treatments focusing on training others (e.g., caregivers) in the delivery of a treatment are not included in the present paper. In recent years, non-pharmacological treatment studies have broadened their focus by targeting individuals in the pre-dementia stages, based on evidence on dementia risk and modifiable lifestyle risk factors (e.g. [11]), as well as an increased focus on the biological definition of AD in pre-dementia stages [12]. The pre-dementia at risk stages as discussed in the current study include those with memory complaints and biomarker evidence for AD as well as those with mild cognitive impairment (MCI). Hence, the NPTs covered in this paper can be relevant in the context of primary, secondary, or tertiary prevention of (objective) cognitive decline and dementia.

**Treatments:** In this paper, we use the term “treatments” or “therapy” rather than “intervention”, in reflection of several principles: 1. While the term “intervention” is sometimes used in the context of both the absence and the presence of a clinical condition, treatment may be more appropriate when a clinical condition is present. 2. The term “intervention” is sometimes used outside of the context of healthcare (e.g., “financial intervention”, “educational intervention”), whereas “treatment” tends to be used more in health-related contexts, such as the context of the current paper. 3. The term intervention may be more appropriate when a wider set of activities, including one or more treatments, are delivered together, and in this sense could be seen as being of a higher order. It is not uncommon to talk about an intervention that includes treatment x or treatment y, but it is less common to talk about a treatment that includes ‘interventions x or y’. 4. Although ‘treatments’ are more common in the context of pharmacological interventions, drugs are referred to as treatments

irrespective of being a 'cure'. Likewise, if the basis for this preference is that pharmacological agents change relevant aspects of underlying pathophysiology, a similar argument can be made in relation to some non-drug treatments (e.g., the anti-inflammatory effects of exercise).

**Non-Pharmacological:** To be included in the current study, the treatment had to explicitly target either cognitive processes or cognition in an everyday context as a primary or secondary aim, and the link to ageing needed to be clear. Additional outcomes may or may have not been addressed as treatment targets. The term 'non-pharmacological' suggests that every treatment that is not a pharmaceutical drug [13] could be considered appropriate. Importantly, the term NPTs only defines what treatments *are not* covered by this title and says nothing about the treatments that *are* covered by this title. It does not seem to be an ideal place to start an effort to define what it is that this paper is concerned with. However, the main feature that could be said to be common to the treatments covered in this paper is that they are non-drug treatments. Alternative terms sometimes used, such as "psychosocial" or "behavioral" treatments are also unsatisfactory as several candidate treatments that might be appropriate in this paper do not seem to be well-captured by these terms (e.g., physical activity, dietary treatments, light-therapy, brain stimulation, etc.). The class of treatments that could be considered appropriate in our context includes a very wide range of treatments, of various degrees of specificity in terms of features or ingredients, action mechanisms, and targets. The term NPTs/NPIs is also broad enough to encompass treatments that are often referred to as complementary and alternative medicines (e.g., Reiki, Tai Chi), as well as treatments in which the target is someone other than the person with or at risk of cognitive decline (e.g., family members, caregivers, GPs, etc.), and treatments focusing on training others (e.g., caregivers) in the delivery of a treatment. Non-drug treatments are typically complex, and several approaches could be used to try and meaningfully group such treatments, including by professional discipline (e.g., psychological treatment, occupational therapy treatment), WHO classification of functioning (i.e., impairment, disability, classification), or by the target symptoms (e.g., wandering, BPSD, cognitive impairment). However, it seems impossible to propose a grouping/classification framework for NPTs that would be entirely satisfactory or mutually exclusive [14-17].

## **A systematic approach to non-pharmacological treatment specification in older people: The Rehabilitation Treatment Specification System (RTSS)**

To address the challenges and difficulties associated with the consistent labelling of NPTs, we adopted an approach that was developed to specifying and classifying rehabilitation treatments: The Rehabilitation Treatment Specification System (RTSS) [18]. Although the RTSS was developed within the framework of rehabilitation, we take the view that ‘rehabilitation’ is appropriate in the current context of treatments, including preventative treatments, to support individuals in minimizing disability and maximizing participation in meaningful life roles. We propose that the field of NPTs in older adults could advance in several ways by drawing on the RTSS framework, including improving treatment development at the protocol stage, treatment reporting, and replication and clinical translation, as well as by improving evidence synthesis through identifying common ingredients and targets across treatments.

According to the RTSS, rehabilitation treatments have a tripartite structure (Figure 2): 1) treatment *targets*, defined as aspects of function the clinician is attempting to change (e.g., improved semantic recall, increased adherence to an exercise regimen); 2) *ingredients*, defined as clinician actions or objects hypothesized to effect that change (e.g., instructions, modeling, coaching); and 3) *mechanisms of action*, the underlying biological or psychosocial mechanisms by which change occurs. Treatment targets are differentiated from *aims*, which are aspects of change that require multiple targets (e.g., improving sleep, increasing social engagement). All targets can be classified into three categories: Organ Functions, Skills and Habits, and Representations (knowledge, beliefs, and attitudes). We grouped NPTs by target category and reported ingredients and ingredient dose where that information was available. As mechanisms of action of NPTs are mostly invisible and incompletely understood (e.g., changes in some aspect of brain function), that element of the RTSS was excluded from this review.

[INSERT FIGURE 2]

An overview of the project timeline and main milestones is shown in Figure 3.

[INSERT FIGURE 3]

## 2. Overview specific treatments

The purpose of this paper is to advance the field of NPTs in aging and dementia by promoting a theoretical framework that can be applied to all NPT research. We did not intend to describe and summarize the evidence for every type of NPT available in the context of aging. The treatments that were included in the current paper were selected on the basis of them being reasonably well-recognized (as reflected in the availability of at least one Cochrane Review covering that treatment), and on the identification of a suitable expert contributor available to support this undertaking. In this paper, we did not include treatments that are exclusively about environmental modification or that primarily target care partners. These are vast areas of research that will be covered in a separate paper. In relation to each specific treatment area covered in this paper, each section is organized as follows:

1. An executive summary, containing treatment definition, a statement regarding the amount and quality of the scientific evidence and the main methodological challenges.

In the appendices, the executive summary is supplemented by:

2. A treatment definition and specification using the RTSS framework as a guide
3. A summary statement regarding the amount and quality of the evidence in relation to key outcomes in one or more populations covered by the current review based on the most authoritative source

4. The main methodological challenges and pressing questions specific to that class of treatment
5. A worked-out treatment specification table for that specific treatment

The treatment specification tables described the general structure of each treatment, as a tool for comparing typical targets and ingredients across treatments. They were not intended to be prescriptive, as with the exception of a few manualized treatments there was wide variation across studies in both the degree to which treatments were specified, if at all, and implementation methods.

An example covering all relevant components above has been included below in relation to cognitive training. For the remainder of the treatments covered, only the executive summaries are included in the paper, with the complete contribution being included in the Appendix.

## **2.1 Cognitive Training**

### **2.1.1 Executive summary**

Cognitive training (CT) involves the formal training of global cognition or specific abilities using standardized tasks [19]. The assumption behind CT is that underlying cognitive processes can be improved or maintained through training [8], and that training-related cognitive gains may prevent, delay, or slow down cognitive and functional decline in older age [20]. High-quality reviews, including two systematic reviews and a systematic overview established that CT leads to moderate improvements in global cognition in people with mild cognitive impairment (MCI) and dementia [21-24]. Evidence for sustained gains, or that go beyond global cognition is of generally low-quality due to high risk of bias in primary trials. Improved implementation of best practice standards in CT research in older age [25], and a better understanding of underlying mechanisms and predictors of gain in individual recipients, are critical research priorities.

### **Treatment specification (See table 1 over page)**

Cognitive training (CT) refers to the formal training of cognitive abilities and processes, usually through repeated practice on standardized tasks designed to reflect specific cognitive domains [8, 19]. Practice may focus on a single or on multiple cognitive domains, it may include advice on the use of, as well as practice with, internal cognitive strategies (e.g., mnemonics), and may be conducted individually or in small groups, and be supervised or unsupervised. A common assumption behind CT is that underlying cognitive processes can be improved or maintained through training, and that training-related cognitive gains may be associated with gains in day-to-day activities, or functional cognition. CT is sometimes confused with the related but distinct approaches of general cognitive stimulation and cognitive rehabilitation (described elsewhere in this paper), and unfortunately these terms are still often used interchangeably [23].

*Common targets and aims of CT.* The primary/immediate target of CT interventions is typically cognition, as reflected in performance on standardized cognitive tests. Depending on the nature of the training, the target may be a specific cognitive ability or process (e.g., divided attention), several inter-related processes, or global cognitive ability. Beyond cognitive ability, additional *aims* of CT treatments have included improvement on measures of mood and wellbeing of the person affected, subjective experience of everyday cognition, functional independence, quality of life, and caregiver burden.

*Broader contexts of CT.* Process-based cognitive training has a long history of use in clinical and healthy populations, particularly with children and older people [26]. In ageing, interest in cognitive training increased at a rapid rate since the early 1980s, with numerous studies published in cognitively healthy people, people with acquired brain injury (e.g., Stroke), and people with neurodegenerative diseases, particularly dementia due to Alzheimer's or vascular disease.

#### **2.1.3 Amount and quality of evidence in relation to dementia and MCI**

Numerous studies and reviews have been published on the effects of cognitive training on cognition and other outcomes in older adults with MCI and dementia. An influential and rigorous meta-analysis from 2017 ([21], AMSTAR=12) found moderate effect on global cognition ( $k=17$ ,  $g=0.35$ , 95% CI= 0.20-0.51), as well as small to moderate effects on several specific cognitive processes, and on

“psychosocial function”. A recently published Cochrane Review of computerized cognitive training (CCT) in people with MCI ([22]; AMSTAR=12.5) that focused on treatments lasting a minimum of 12 weeks, and that applied stricter inclusion criteria and risk of bias rating found, based on meta-analysis of 5 trials, a moderate effect of CCT on global cognition at the end of treatment relative to active control ( $k=5$ ,  $g=-0.53$ , %95 CI= -1.06 to -0.01). Effects of CCT were found in several specific cognitive domains as well (episodic memory, speed of processing, working memory), but not on any non-cognitive outcome, based on a small number of meta-analyzed trials. Regarding people with mild to moderate dementia, a recent Cochrane Review ([23]; AMSTAR=14), found that relative to active or passive control conditions, CT was associated with gains in global cognition ( $k=33$ ,  $g=0.42$ , %95 CI= 0.23 to 0.62), and verbal category fluency ( $k=9$ ,  $g=0.52$ , %95 CI= 0.23 to 0.81) at the end of treatment, and that these gains were maintained in the medium term (up to 12 months post-treatment). CT did not benefit non-cognitive outcomes, and no differences were found when CT was compared with an alternative treatment.

Evidence syntheses efforts of trials of CT in people with MCI and dementia have consistently identified methodological challenges in primary trials, which are often ranked at being at high or unclear risk of bias in several key domains, including lack of randomization concealment, incomplete outcome data, and selective reporting. Large statistical and clinical heterogeneity and imprecision of effect estimates has led authors of recent reviews to grade most of the evidence as being of ‘low’ or even ‘very low’ quality.

#### **2.1.4 Main methodological challenges and the most pressing questions to be addressed**

Consistent implementation of best practice standards in numerous aspects of trial planning (including registration and protocol publication), implementation (including adequate randomization and appropriate control, as well as selection of outcomes and measures), analysis (including dealing with missing data, protocol deviations, and multiple comparisons), and reporting (clear, detailed and transparent description of all key design features), remain significant barriers in the field of CT.

The methodological challenges discussed above notwithstanding, the weight of the evidence supports the view that structured process-based cognitive training leads to at least modest

improvements in cognitive test performance in people with MCI and dementia, and that these improvements may be maintained over a short to medium period. What is now required is a sustained effort to improve our understanding of how to develop more personalized CT treatments that can be better integrated with everyday life and meaningful everyday activities, so that ongoing engagement is more likely and that transfer of gains from performance on standard tests of cognition to relevant functional domains is enabled. In addition, improved knowledge of the structural and functional effects of CT in key brain regions and networks would help ensure that task design and selection, as well as dosing parameters, are informed by such changes.

Author Manuscript

This article is protected by copyright. All rights reserved.



**Table 1.** Specification of cognitive training against the RTSS framework.

Cognitive Training: Ten-week home-based multidomain computer-based cognitive training for adults with Mild Cognitive Impairment				
Target population	Target	Target Group (Type)	Ingredients	
Older adults with mild cognitive impairment	Increased knowledge and understanding of age-related changes in cognitive abilities and links with functional independence	R(D)	<ul style="list-style-type: none"> <li>Information about age-related changes in cognition included in Participant Information Sheet and provided verbally by researcher</li> <li>Additional written information about various cognitive abilities and their links with everyday behaviors</li> </ul>	<ul style="list-style-type: none"> <li>Wh...</li> <li>stud...</li> <li>We...</li> </ul>
	Increased capability to use the online training platform	S(D)	<ul style="list-style-type: none"> <li>Face-to-face orientation to online training platform</li> <li>Demonstration of online training platform provided by clinician/trained research staff</li> <li>Provision of written manual describing all necessary steps to access and complete a training session</li> <li>Phone-based troubleshooting/technical support</li> </ul>	<ul style="list-style-type: none"> <li>On...</li> <li>On...</li> <li>On...</li> <li>On...</li> </ul>
	Improved performance on a composite global measure of cognitive function	S(D)	<ul style="list-style-type: none"> <li>Participant to practice on a set of 20-30 computerized tasks targeting multiple cognitive domains</li> </ul>	<ul style="list-style-type: none"> <li>30 t...</li> <li>wee...</li> </ul>
	Motivation to adhere to the treatment	R(V)	<ul style="list-style-type: none"> <li>Verbally delivered information about potential short and long-term gains associated with process training</li> <li>Feedback on performance delivered by the online training platform</li> <li>Feedback on performance delivered over the phone by research staff</li> <li>Written behavioral contract to increase commitment to the training</li> <li>Barrier identification with problem solving</li> </ul>	<ul style="list-style-type: none"> <li>On...</li> <li>Aft...</li> <li>On...</li> <li>On...</li> <li>On...</li> </ul>

1 **Executives summaries for remaining treatments**

2 **2.2 Cognitive Rehabilitation**

3 Cognitive rehabilitation (CR) is a goal-oriented, problem-solving behavioral therapy aimed at  
4 optimizing ability to function in everyday life in relation to the person’s needs, wishes and  
5 preferences [27]. Robust evidence including findings from two large trials supports the potential of  
6 CR to improve management of functional disability [28, 29]. Evidence from pilot studies [30, 31] and  
7 qualitative evaluations [32] suggests that people with dementia and caregivers can experience wider  
8 benefits such as improved adjustment or coping, but these have not yet been captured  
9 quantitatively in the larger trials. The typical length of follow-up in trials precludes identification of  
10 long-term benefits. Future efforts should focus on optimizing outcome measurement, including  
11 longer follow-up periods in trials, and implementing CR into healthcare provision (see Supplemental  
12 Text 2 and RTSS Table 2).

13

14 **2.3 Cognitive Stimulation Therapy**

15 Cognitive Stimulation Therapy (CST) is a brief, manualized intervention, based on the theory that  
16 appropriate and targeted mental stimulation can lead to the development of new neuronal  
17 pathways. CST aims to improve cognitive function, as well as quality of life and mood, through  
18 themed group activities, such as discussing current affairs, which implicitly stimulate memory,  
19 executive functioning and language skills. There is a large, international evidence-base for group CST  
20 demonstrating a significant beneficial effect on cognition and quality of life in dementia [33]. A  
21 Cochrane systematic review of 15 RCTs found consistent benefits of CST on cognitive function [34]. A  
22 systematic review of 12 studies evaluating the UK CST protocol found improvements in cognition,  
23 quality of life, depression and impact on caregivers [35]. Further research efforts may include  
24 investigating the relationship between adherence to outcome as well as the effectiveness of  
25 individual CST delivered by non-family caregivers (see Supplemental Text 3 and RTSS Table 3).

26

27 **2.4 Nutritional treatments**

28 Nutritional treatments aim to modify dietary intake of micronutrients (vitamins and minerals) and/or  
29 macronutrients (proteins, fats, carbohydrates) through specific supplements or in combination

1 through diet [36, 37]. Adequate nutrition is essential for brain health because of its involvement in  
2 biological pathways that reduce oxidative stress and inflammation, promote vascular health, as well  
3 as improve neuronal cell signaling and function of neuronal cells [38-40]. Despite limited evidence on  
4 the effect of nutritional treatments on cognitive outcomes, and significant methodological  
5 challenges, data is promising [41-47]. Single trials have shown a beneficial effect of B vitamins  
6 supplementation on memory performance in MCI patients with high homocysteine [41], as well as  
7 improvements in cognitive performance by supplementation of DHA and EPA, and flavonols [42-45].  
8 Large trials on vitamin E supplementation demonstrated delayed progression in functional decline  
9 and AD [46, 47]. Future research should replicate these findings by focusing on conducting clinical  
10 trials in sufficient size and duration, as well as rigorous procedures for randomization and blinded  
11 testing (see Supplemental 4).

12

### 13 **2.5 Physical exercise training**

14 Physical exercise training is based on planned and/or structured activity which may be aerobic  
15 exercise, resistance training [48] or a combination (multimodal) or mind-body exercise (e.g. Tai Chi).  
16 The evidence for a positive effect of aerobic training on global cognition is growing with consistent  
17 medium effects sizes reported from systematic reviews and meta-analyses [49-51]. Resistance  
18 training usually requires supervision and therefore more resources and intensive treatments to  
19 achieve effective adherence. While promising, evidence on this type of training has yet to reach the  
20 same consistency, quality and volume as that of aerobic training. Future research should investigate  
21 whether exercise modes are domain-specific and identification of strategies to enhance adherence  
22 to exercise training is warranted (see Supplemental Text 5 and RTSS Table 4).

23

### 24 **2.6 Sleep treatments**

25 Insomnia is defined as problems with sleep quality or quantity, including difficulty initiating sleep,  
26 repeated prolonged awakenings, and/or nonrestorative sleep [52, 53]. Several meta-analyses of  
27 Cognitive-Behavioral Therapy for Insomnia (CBT-I) support the finding that sleep disturbance is very  
28 amenable to change in both young and older adults, with treatment resulting in robust  
29 improvements in sleep quantity and quality [54-56]. Future efforts should study on the neuronal

1 overlap and causal mechanisms between sleep disturbance and cognitive decline in individuals  
2 ranging from cognitively normal to impaired, in order to decide which approaches should be used for  
3 which populations and at which point in time.

4 In addition to insomnia, sleep disturbances in persons with dementia (PWD) also include  
5 hypersomnia, excessive motor activity at night, and hallucinations or other behavioral problems.  
6 Sleep specialists aim to target nocturnal neurocognitive symptoms in PWD through implementation  
7 of sleep promotion strategies (e.g. bright light, regulation of sleep-wake schedules, decreasing  
8 arousal, increasing daytime activity) based upon CBT of sleep. While studies have established the  
9 effectiveness of various environmental and multi-component treatments to improve sleep in PWD  
10 [57-62], there are currently no meta-analyses or systematic reviews of CBT-I in those with MCI or  
11 dementia. Specific CBT-related methodological challenges included lack of standard treatment  
12 components and measurements and need for caregivers who can oversee treatment  
13 recommendations and sleep assessments. Future research should focus on the understanding the  
14 role of sleep disturbances in the pathogenesis of dementia and the underlying mechanisms of sleep  
15 and cognitive decline, as well as how dementia diagnostic subtypes and age of onset may impact  
16 treatment response (see Supplemental Text 6 and 7, and RTSS Table 5).

## 18 **2.7 Meditation**

19 Meditation refers to a family of emotional and attentional regulatory training exercises [63, 64].  
20 Meditation training programs, usually including sessions with an instructor as well as daily home  
21 practice, have been shown to improve cognition, wellbeing and health in older age and may  
22 contribute to delaying the onset of dementia [65-67]. Potential mechanisms underlying the effect of  
23 meditation include effects on inflammation, stress and emotion regulation, brain microstructure  
24 and/or macroscopic brain structure, brain glucose metabolism and brain connectivity and effects on  
25 telomeres length and telomerase activity [67-70]. There are currently no meta-analyses or  
26 systematic reviews specifically focused on meditation as a single domain treatment for MCI and  
27 dementia. Though there is limited formal evidence, pilot RCTs and cross-sectional studies showed  
28 effects on cognition [71, 72], psycho-affective factors [71, 73], sleep quality [73], and quality of life  
29 [73, 74]. Future research should include longitudinal studies and RCTs, with large samples and using

1 clinically meaningful biological and neuroimaging biomarkers (see Supplemental Text 8 and RTSS  
2 Table 6).

3

## 4 **2.8 Reminiscence therapy**

5 Reminiscence therapy is the recollection and sharing of personal memories and experiences. It aims  
6 to promote cognition, communication, identity, mood, social connectedness, mental health,  
7 wellbeing and quality of relationships [75, 76]. It can be offered individually or in groups. Recently,  
8 systematic reviews and meta-analyses [77-80], and (an abridged) Cochrane review were published  
9 [76, 81]. Evidence showed small significant positive effects on quality of life, mood, behavioral and  
10 psychological symptoms of dementia (BPSD), cognition and communication in people with mainly  
11 mild to moderately severe dementia. Effects differed depending on treatment modality and setting.  
12 Future efforts should include large RCTs with detailed descriptions of the treatment protocols,  
13 targets, aims, and target groups (see Supplemental Text 9 and RTSS Table 7).

14

## 15 **2.9 Music-based treatments**

16 Music-based treatments are classified as active or receptive musical activities that aim to address  
17 multiple non-musical outcomes (e.g. cognitive, psychosocial, communication and physical goals),  
18 often simultaneously. Active treatments include instrument playing, singing, songwriting, and  
19 moving to music. Receptive treatments involve listening to recorded or live music. *Music therapy*  
20 *treatments* (goal-based therapeutic musical interaction with a trained therapist), are distinguished  
21 from *music activities* that can be implemented by other clinicians, caregivers or self-administered. A  
22 recent Cochrane review summarized the effect of multiple RCTs examining both active and receptive  
23 music treatments and reported evidence for reductions in depression and overall behavioral  
24 problems, but no effect on agitation, and low quality evidence for reductions in anxiety and quality  
25 of life and little to no effect on cognition [82]. For other areas, such as anxiety and social behavior,  
26 the Cochrane review found not enough evidence to determine effects. Other recent reviews have  
27 found evidence that music therapy is effective in reducing agitation, anxiety, depression and other  
28 neuropsychiatric symptoms [83-85]. There is disagreement between some published meta-analyses  
29 on whether active or receptive treatments are more effective for specific outcomes. The low quality

1 of the current evidence highlights that improvements for future research are necessary, most  
2 specifically improving design quality and comparing different music-based treatments (receptive  
3 versus active) and dosage (see Supplemental Text 10 and RTSS Table 8).

## 4 5 **2.10 Communication treatments**

6 Communication interventions target a construct referred to as “quality of communication life”,  
7 defined as the extent to which a person’s communication acts allow a meaningful participation in life  
8 situations [86]. Communication treatments aim to maintain or improve quality and quantity of  
9 meaningful communication interactions. These treatments can be divided into direct and indirect  
10 treatments. Direct treatments are primarily language stimulation tasks and activities, delivered  
11 individually or in groups. Indirect treatments include training family and professional carers in  
12 strategies for effective communication, modifying environments to facilitate communication, and  
13 developing therapeutic routines and activities that promote communication. A current challenge is  
14 the tendency for late (or no) recognition of communication problems in MCI and dementia. The level  
15 of evidence is currently limited due to a lack of controlled studies, and future efforts should focus on  
16 this (see Supplemental Text 11 and RTSS Table 9).

## 17 18 **2.11 Multisensory treatments**

19 Multisensory treatments stimulate the senses (sight, hearing, taste, touch, smell) to compensate for  
20 sensory deprivation or to restore an imbalance such as suboptimal pacing of stimulating and calming  
21 sensory input [87, 88]. These treatments mostly aim to improve behavior, quality of life, wellbeing or  
22 functioning and are often suitable for moderate dementia. Snoezelen and sensory gardens involve  
23 supervised presence in environments equipped with tools to stimulate senses, and Sonas is a  
24 structured group program to stimulate all senses. Although all of these treatments have been  
25 studied in some RCTs, the treatments were heterogeneous and study samples small [89-94]. Taken  
26 together, the evidence base for effects is still modest. At this point, well-designed RCTs that allow  
27 studying subgroup effects are necessary to advance the field (see Supplemental Text 12 and RTSS  
28 Table 10).

## 2.12 Occupational therapy

The primary aim of occupational therapy is to optimize occupational performance by enabling people to participate in the activities that they want, need, or are expected to do [95]. One of the theoretical models is the person-environment-occupation model [96], which portrays the relationship between the capabilities and characteristics of the person: the physical, social and cultural, environment; and the target occupation. The level of evidence for some outcomes is considered 'moderate' with a number of high quality RCTs, which were supportive of improvements in ADL and quality of life and reductions in problem behavior [97]. Key challenges for the field of occupational therapy include determining the optimal characteristics of the treatment, dose, methods of service delivery and subgroups most likely to benefit from treatment(see Supplemental Text 13 and RTSS Table 11).

## 2.13 Neuromodulation

Neuromodulation involves the introduction of energy (e.g., electrical, magnetic) into the brain with the goal of altering neurophysiology. Treatments include transcranial magnetic stimulation (TMS); transcranial direct current stimulation (tDCS). This treatment is currently not yet clinically approved for the use in cognitive deficits. Existing meta-analyses and reviews provide conflicting evidence for the effects of neuromodulation in those across the dementia spectrum but are limited by a small number of primary research studies with small sample sizes [98, 99]. Research into neuromodulation needs focus on dosing parameters, including dose-response relationships, and the combination with and timing of other (non)pharmacological agents. This will likely reduce heterogeneity in response and facilitate clinical translation efforts (see Supplemental Text 14 and RTSS Table 12).

## 3. General methodological considerations

Several NPTs show a clear therapeutic potential, but the depth and breadth of the evidence base so far varies across the different treatments. The body of evidence concerning cognitive training [21] and physical exercise [10] appears to be more advanced relative to other treatments covered. A common thread through most of the primary research and associated systematic reviews is the need

1 to improve the quality, transparency and clinical relevance of NPT trials in aging and dementia.  
2 Realizing the potential of NPTs will strongly depend on future trials being developed against a well-  
3 articulated rationale, a stronger focus on hypothesis testing, and trials being more rigorously  
4 designed. Critical elements including treatment development, trial design and outcome  
5 measurement should be carefully considered early in the planning phase to minimize risk of bias and  
6 to maximize generalizability of findings. Below, we provide recommendations concerning some of  
7 the key design questions that need to be considered by those designing such trials (for an overview,  
8 see Figure 4 and Table 2).

9  
10 [INSERT FIGURE 4]

11  
12 Existing evidence and pilot work should inform key factors such as treatment content and dose,  
13 ideally based on systematic reviews that investigate the moderating effects of design factors. The  
14 dose (intensity, frequency and length) should consider not only possible dose responsiveness, but  
15 also matters of compliance and adherence (in particular for self-administered and unsupervised  
16 treatments) that should be measured using reliable methods [100, 101]. Ideally, a small-scale pilot  
17 study should be conducted to obtain the information before a ‘Phase I study’ is carried out. A key  
18 issue of increasing importance in treatment development is creating opportunities for key  
19 stakeholders (patients, care partners, and clinicians) to be involved and provide input as appropriate  
20 into the development of the treatment protocol, and through the course of its evaluation.

21 Treatment targets (e.g., cognition, behavior, or risk factor) and their operationalization should occur  
22 at the start of the planning process. Key questions to ask are whether the treatment is expected to  
23 affect proposed biological, clinical, or functional target(s) and aims, and the RTSS framework can be  
24 useful in thinking through these issues. Whether existing, validated measures of the proposed  
25 targets are available and can be used, and how frequently outcomes will be assessed are questions  
26 of paramount importance. Where possible, selection of outcome measures should be based on  
27 standard diagnostic techniques and ensure measures have evidence of adequate psychometric  
28 properties, including test-retest reliability, validity, and be sensitive enough to detect change.



1

2 Researchers should ensure they carefully consider the research question(s) they would like the trial  
3 to address, and whether these imply trials that emphasize feasibility/acceptability of a treatment,  
4 dose-response issues, superiority or non-inferiority in relation to another treatment, an active  
5 control condition, or treatment as usual. These research questions are of great importance and  
6 should directly impact decisions regarding the most appropriate trial design. In addition to  
7 determining whether a randomized controlled design is feasible and appropriate, consideration  
8 should be given to whether assignment to treatment conditions, and outcome evaluations can be  
9 blinded. Moreover, considerations should include whether experimental and comparison conditions  
10 should take the form of parallel arms, cross-over or delayed start to one arm or a factorial  
11 randomization to examine more than one treatment.

12 If hypotheses are made regarding more than one main outcome, it is important to  
13 determine whether the outcomes should be treated as co-primary, or whether one outcome should  
14 be considered primary and another secondary. These distinctions between primary and secondary  
15 outcomes are important for a range of reasons, including for establishing issues related to statistical  
16 power and in order to interpret the clinical relevance of the finding. Putative effect moderators need  
17 to be carefully considered in order to maximize the generalizability and clinical relevance of the  
18 findings (positive or negative).

19

20 **3.1 Essential ingredients for the next generation of robust non-pharmacological trials**

21 A power calculation should be conducted to inform recruitment and this should be based on the  
22 expected level of change in the primary outcome(s) based on pilot studies and/or past literature.  
23 The sources used to estimate the expected treatment effect for power calculations (e.g. studies  
24 which provided the information on expected changes and its standard deviation or coefficient and  
25 its standard error) need to be clearly stated. In recent years, a growing number of trials include  
26 measurements of digital biomarkers (e.g., motion sensors). Issues related to the frequency of such  
27 measurements (e.g., continuously, daily, monthly, etc.) and processing of the data could have critical  
28 implications for power estimates [102] and this needs to be carefully considered, especially if such  
29 markers are used as trial outcomes. Power and sample-size targets should also take into account

1 expected rates of attrition, death or discontinuation. If attrition is likely to be greater in one of the  
2 trial arms than other arms, this needs to be taken into account, and similarly if recruitment to one of  
3 the trial arms is expected to be more challenging, this too should be taken into account at the  
4 protocol stage. The Consolidated Standards of Reporting Trials Statement (CONSORT, [103]), initially  
5 developed in the context of biomedical trials, was recently extended to accommodate the trials in  
6 behavioral and social sciences (CONSORT-SPI, [104]). Researchers are encouraged to consider the  
7 items in the CONSORT-SPI statement at the protocol planning phase to make sure that all the basic  
8 requirements in RCTs are covered. Intention-to-treat (ITT) analyses are the gold standard because  
9 they eliminate potential selection bias associated with only analyzing data from participants who  
10 adhered to their assigned treatment arm. However, CONSORT guidelines recommend that both ITT  
11 and per protocol (PP) analyses be reported for all outcomes so that readers can interpret the effect  
12 of a treatment in a more informed manner [105]. This practice is particularly relevant in NPT trials as  
13 personal preferences and individual differences often affect adherence levels and this has  
14 implications to whether a treatment can be sustained in a longer term. Understanding factors  
15 associated with treatment adherence is critical in considering the real-world application of a  
16 treatment and “dose-response” effects. The selection process from the ITT sample to the PP sample  
17 and the difference in effect sizes between the two analyses could provide key information in  
18 estimating translational effects or sustainability of a treatment in the real world. Planned subgroup  
19 and adjusted analyses should be clearly outlined at the protocol stage.

20 Finally, the planned trial should be considered pragmatically in a real-world context, in  
21 particular with regards to the (recruitment of) the target population. Regulatory aspects need to be  
22 taken into consideration, with the local regulatory agency for drug and device trials, the University or  
23 sponsor’s research governance offices as good starting points for this information.

24  
25

1 **Table 2:** Checklist for the design of a non-pharmacological treatment trial

2

Stage	Checklist items	Considerations
(A)	<ol style="list-style-type: none"> <li>1. Duration of trial follow-up</li> <li>2. Population selection</li> </ol>	Duration of follow-up should be reasonable in view of past studies and evidence. For the population selection, consider whether targeted sample characteristics are justifiable, in terms of age range, gender, genetics and other characteristics.
(B)	<ol style="list-style-type: none"> <li>1. Conceptualization of mechanisms</li> </ol>	Consider the alignment between treatment target and outcomes
(C) (D)	<ol style="list-style-type: none"> <li>1. Operationalize treatment targets</li> <li>2. Dose considerations</li> </ol>	For specifying treatment targets, consider the use of the RTSS framework. For dose considerations, adequate dosing should be carefully considered, or multiple arms with different dosing might be part of the study design.
(E) (F)	<ol style="list-style-type: none"> <li>1. Operationalize outcomes.</li> <li>2. Trial intervals and duration of follow-up</li> </ol>	<p>Adequately selected and operationalized outcomes are key to a treatment trial. Primary outcomes, co-primary outcomes, dual primary outcomes, exploratory outcomes, secondary outcomes should be carefully considered. For the operationalization of the outcomes it is recommended to use already validated measures, taking into account whether the scale is validated in the population of interest, as well as evidence for the sensitivity to capture changes over time (longitudinal validation) in relationship to the proposed assessment time period. When creating new outcome measures, consider an independent validation pilot study when planning your study.</p> <p>When planning trial intervals, consider how often the outcomes should be measured, based on past evidence. Clearly monitor and define adherence (e.g. days completed?, % of duration completed?).</p>
(G)	<ol style="list-style-type: none"> <li>1. Statistical analyses</li> </ol>	<p>Carefully consider what analytical models are best suited for establishing the hypothesized mechanisms, as well as the approach to minimize the required sample size. Consider whether changes are expected in a linear or non-linear fashion.</p> <p>Define threshold of statistical significance (consider multiple comparison adjustment) and define minimum effect size upfront. Consider potential drop out mechanisms, and what kinds of sensitivity analyses need</p>

---

to be proposed.

Intention to treat (ITT) analyses vs. modified ITT analyses (e.g., include those with at least one follow-up) vs. Per Protocol Analyses (PP). Both analyses are recommended with ITT analyses being the gold standard. Clearly propose upfront what type of analyses will be conducted.

Include sample size estimates and simulations. Is the sample size proposed adequate AND feasible, provide evidence and justifications.

- 
- (H)
1. IRB approval
  2. Clinicaltrials.gov registration

Consider how long will it take to receive ethical approval, whether you need site specific approvals (multicenter studies), and other issues such as sponsor approval, confirmation of insurance, approval from healthcare providers or regulatory bodies for allied healthcare professionals, approvals from consumer groups, inclusion of people with lived experience on research committees, national or international approval or validation for device trials, secure data collection and data management plans.

---

1  
2

#### 4. Concluding remarks

The aim of this paper was to summarize the body of work available in relation to key types of NPT in the context of aging and dementia studies; identify key challenges for different NPTs; and provide methodological guidelines for the design of future trials of NPTs. Our work thereby represents an important step in the process of advancing the theoretical and methodological rigor of research into NPTs.

Numerous treatment approaches fall under the umbrella term ‘NPT’. The current paper focused on a sample of these approaches for which there is a relatively robust body of evidence, and applied the RTSS framework to identify targets, ingredients, and dosing parameters for these treatments. The importance of developing practices that promote the replicability of treatment studies cannot be overstated [106], and to do that we need systematic descriptions of those practices [18]. The work in the present paper underscores some of the challenges and opportunities associated with using a single theoretical framework to describe, specify and prescribe very diverse treatments. When examined using the RTSS framework, it can be clearly seen that many or most treatments involve targets that fall primarily into the skills and the representations target groups. This is not surprising given that NPTs typically (with some exceptions) don’t have organ functions as their direct targets. The RTSS framework also revealed themes across treatments that go by different names and are offered by different healthcare providers, including themes in targets (e.g., improving memory), and ingredients (e.g., physical and mental exercise in MCI, environmental modification in dementia). Articulating core targets, ingredients, and dosing parameters of given treatments was often challenging. Ingredients and dosing parameters were often omitted from treatments described in the literature, or described only in general terms (e.g., “enabling ingredients”, weeks of treatment). Likewise, targets of a treatment were not always stated in published reports. Even for the expert contributors, distinguishing between treatment targets and downstream aims required some effort. A benefit of using the RTSS in this project was that it prompted critical thinking and discussion about what treatments were actually intended to achieve, and researchers’ theories about what aspects of treatment would effect that change.

Review of the evidence in relation to the different NPTs shows that while treatments may be effective in bringing about change in their immediate targets, effectiveness for changing downstream aims is less conclusive. The RTSS was helpful here as well, as it revealed treatments in

1 which the primary outcome was actually an *aim* rather than the *target* of the treatment. A common  
2 example was cognitive training-type treatments that were hypothesized to improve everyday  
3 cognitive function, but had actual treatment targets like “improved accuracy of recall” on memory  
4 tasks, used ingredients designed to improve recall on those tasks, and measured outcomes via  
5 scores on memory tests and subjective everyday memory measures. Results of many studies showed  
6 improvements on tests but not in everyday life. Those results are not surprising because change in  
7 everyday life requires different ingredients, including ingredients and targets related to factors like  
8 family education and participant awareness. A treatment can therefore be dismissed as ineffective  
9 when the problem is a mismatch among ingredients, targets, and outcome measures. Using the RTSS  
10 can promote a better match across these variables and clearer specification of what the treatment is  
11 intended to achieve, and thus help reveal treatment effects. A further point is that is also evident  
12 that research to date has focused predominantly on the well-established clinical stages of MCI and  
13 dementia, with a very limited literature evaluating the benefits from NPTs on people with SCD.

14         Given accumulated supportive evidence in relation to some treatments (e.g. cognitive  
15 training, music therapy), it is important that researchers collaborate effectively with industry  
16 partners, government and non-government healthcare organizations to design and carry out  
17 rigorous yet pragmatic implementation studies embedded within existing service frameworks. Such  
18 research should also aim to understand effective methods to shift attitudes of prescribing clinicians,  
19 so that appropriate NPTs be offered to individuals along the cognitive ageing continuum. These  
20 studies are also important to further our understanding of the efficacy of different NPTs in the  
21 context of the etiological heterogeneity of dementia and MCI syndromes. Even in areas where the  
22 research is not mature enough to move to implementation studies (e.g., Mindfulness), increasing  
23 efforts should be now directed toward a better understanding of person and treatment related  
24 factors that moderate treatment efficacy and predict treatment response at the level of the  
25 individual patient. Common barriers that were reported included the inadequacy of reporting of  
26 relevant data regarding treatment adherence, motivation, and various personal characteristics that  
27 are likely to play a role in treatment adherence, persistence, and response. Along with improved  
28 specification of treatments, the field of NPTs will require to continue improving on reporting  
29 standards, to make sure that evidence can be adequately synthesized, and that replication efforts  
30 are not wasted.

1 The current study has several limitations. First, although we intended to provide a  
2 comprehensive overview of NPTs in aging and dementia, we acknowledge that several treatment  
3 areas were not covered. This was based on our decision to only include treatments for which  
4 substantial research evidence was available, as reflected primarily by the availability of at least one  
5 Cochrane review. Emerging treatment approaches for which there is growing interest, such as  
6 multidomain lifestyle interventions like the FINGER trial [107], and specific diets such as the  
7 Mediterranean and MIND diet [108] were therefore not included. Regarding Mindfulness, we are of  
8 the opinion that the current work can aid in an improved understanding of person and treatment  
9 related factors. A second limitation concerns the RTSS framework terminology used in the current  
10 paper which in some cases might differ from conventions in this research field (e.g. 'target' instead  
11 of 'outcome'). In our view, adopting an existing and well-established framework outweighed those  
12 limitations.

13 The many advantages of NPTs are well recognized. We hope that the theoretical framework  
14 proposed and the methodological guidelines offered in the current study would help researchers  
15 designing the next generation of NPT studies in such a way that more reliable evidence and evidence  
16 synthesis efforts are produced, and that the optimal approaches to NPTs, tailored to the specific  
17 characteristics of individuals, will be developed and lead to meaningful outcomes in the lives of  
18 people with dementia, or at risk of dementia.

1 **ACKNOWLEDGEMENTS**

2

3 The NPI-PIA executive committee is grateful to the many contributors who have worked closely with  
4 us on this project. We would like to acknowledge in particular the guidance and vision of Prof Linda  
5 Clare and Henry Brodaty. We are very grateful to Prof Lyn Turkstra for generously giving much of her  
6 time to help the section contributors develop their work against the RTSS framework and for  
7 providing numerous insights and comments on the paper. We are grateful to the wider NPI-PIA  
8 membership and ISTAART for supporting and encouraging this effort.

9

10 This work is dedicated to the memory of Dr. Martha Clare Morris, a visionary researcher who shaped  
11 much of the work on the links between nutrition and dementia and who led the nutrition section of  
12 this paper. We are confident that she would have been proud of the outcome.



## References

1. Alzheimer's, A., *Alzheimer's Disease Facts and Figures*. Alzheimer's & Dementia, 2015. **11**(3): p. 332-+.
2. Prince, M., et al., *World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future*. 2016.
3. APA, A.P.A., *Diagnostic and statistical manual of mental of mental disorders, Fifth Edition (DSM-V)*. 2013, Washington, D.C.: American Psychiatric Association.
4. Petersen, R.C., *Mild cognitive impairment*. CONTINUUM: Lifelong Learning in Neurology, 2016. **22**(2 Dementia): p. 404.
5. Jessen, F., et al., *A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease*. Alzheimer's & Dementia, 2014. **10**(6): p. 844-852.
6. Scales, K., S. Zimmerman, and S.J. Miller, *Evidence-Based Nonpharmacological Practices to Address Behavioral and Psychological Symptoms of Dementia*. Gerontologist, 2018. **58**(suppl\_1): p. S88-S102.
7. Olazaran, J., et al., *Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy*. Dement Geriatr Cogn Disord, 2010. **30**(2): p. 161-78.
8. Bahar-Fuchs, A., L. Clare, and B. Woods, *Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia*. Cochrane Database Syst Rev, 2013(6): p. CD003260.
9. van der Steen, J.T., et al., *Music-based therapeutic interventions for people with dementia (Review)*. Cochrane Database of Systematic Reviews, 2017. **Issue 5. Art. No.: CD003477**.
10. Young, J., et al., *Aerobic exercise to improve cognitive function in older people without known cognitive impairment*. Cochrane Database of Systematic Reviews, 2015(4).
11. Livingston, G., et al., *Dementia prevention, intervention, and care*. Lancet, 2017. **390**(10113): p. 2673-2734.
12. Jack Jr, C.R., et al., *NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease*. Alzheimer's & Dementia, 2018. **14**(4): p. 535-562.
13. Pharmacists Pharma Journal. <http://www.pharmacistspharmajournal.org/>. 2010, November 10 [cited 2019 May 14th]; Available from: [http://www.pharmacistspharmajournal.org/2010/11/definitions-of-drug-radioactive-drug\\_11.html#.XNoXoFszaUk](http://www.pharmacistspharmajournal.org/2010/11/definitions-of-drug-radioactive-drug_11.html#.XNoXoFszaUk).
14. Michie, S. and C. Abraham, *Advancing the science of behaviour change: a plea for scientific reporting*. Addiction, 2008. **103**(9): p. 1409-10.
15. Michie, S. and A. Prestwich, *Are interventions theory-based? Development of a theory coding scheme*. Health Psychol, 2010. **29**(1): p. 1-8.
16. Michie, S., M.M. van Stralen, and R. West, *The behaviour change wheel: a new method for characterising and designing behaviour change interventions*. Implement Sci, 2011. **6**: p. 42.

- 1 17. Hart, T., et al., *Toward a theory-driven classification of rehabilitation treatments*. Archives of  
2 physical medicine and rehabilitation, 2014. **95**(1): p. S33-S44. e2.
- 3 18. Hart, T., et al., *A theory-driven system for the specification of rehabilitation treatments*.  
4 Archives of physical medicine and rehabilitation, 2019. **100**(1): p. 172-180.
- 5 19. Clare, L., et al., *Cognitive rehabilitation and cognitive training for early-stage Alzheimer's*  
6 *disease and vascular dementia*. Cochrane Database Syst Rev, 2003(4): p. CD003260.
- 7 20. Gates, N.J. and P. Sachdev, *Is Cognitive Training an Effective Treatment for Preclinical and*  
8 *Early Alzheimer's Disease?* Journal of Alzheimer's Disease, 2014.
- 9 21. Hill, N.T., et al., *Computerized Cognitive Training in Older Adults With Mild Cognitive*  
10 *Impairment or Dementia: A Systematic Review and Meta-Analysis*. Am J Psychiatry, 2017.  
11 **174**(4): p. 329-340.
- 12 22. Gates, N.J., et al., *Computerised cognitive training for preventing dementia in people with*  
13 *mild cognitive impairment*. Cochrane Database Syst Rev, 2019. **3**: p. Cd012279.
- 14 23. Bahar-Fuchs, A., et al., *Cognitive training for people with mild to moderate dementia*.  
15 Cochrane Database Syst Rev, 2019. **3**: p. Cd013069.
- 16 24. Gavelin, H.M., et al., *Cognition-oriented treatments for older adults: A systematic overview of*  
17 *systematic reviews*. Neuropsychol Rev, 2020. **10**.
- 18 25. Simons, D.J., et al., *Do "brain-training" programs work?* Psychological Science in the Public  
19 Interest, 2016. **17**(3): p. 103-186.
- 20 26. Katz, B., P. Shah, and D.E. Meyer, *How to play 20 questions with nature and lose: Reflections*  
21 *on 100 years of brain-training research*. Proceedings of the National Academy of Sciences,  
22 2018. **115**(40): p. 9897-9904.
- 23 27. Clare, L., et al., *Cognitive rehabilitation, self-management, psychotherapeutic and caregiver*  
24 *support interventions in progressive neurodegenerative conditions: A scoping review*.  
25 NeuroRehabilitation, 2018. **43**(4): p. 443-471.
- 26 28. Amieva, H., et al., *Group and individual cognitive therapies in Alzheimer's disease: the ETNA3*  
27 *randomized trial*. Int Psychogeriatr, 2016. **28**(5): p. 707-17.
- 28 29. Clare, L., et al., *Individual goal-oriented cognitive rehabilitation to improve everyday*  
29 *functioning for people with early-stage dementia: A multicentre randomised controlled trial*  
30 *(the GREAT trial)*. Int J Geriatr Psychiatry, 2019. **34**(5): p. 709-721.
- 31 30. Clare, L., et al., *Goal-oriented cognitive rehabilitation for people with early-stage Alzheimer*  
32 *disease: a single-blind randomized controlled trial of clinical efficacy*. Am J Geriatr Psychiatry,  
33 2010. **18**(10): p. 928-39.
- 34 31. Hindle, J.V., et al., *Goal-orientated cognitive rehabilitation for dementias associated with*  
35 *Parkinson's disease-A pilot randomised controlled trial*. Int J Geriatr Psychiatry, 2018. **33**(5):  
36 p. 718-728.
- 37 32. Clare, L., et al., *Goal-oriented cognitive rehabilitation for early-stage Alzheimer's and related*  
38 *dementias: the GREAT RCT*. Health Technol Assess, 2019. **23**(10): p. 1-242.
- 39 33. Orrell, M., et al., *Maintenance cognitive stimulation therapy for dementia: single-blind,*  
40 *multicentre, pragmatic randomised controlled trial*. Br J Psychiatry, 2014. **204**(6): p. 454-61.

- 1 34. Woods, B., et al., *Cognitive stimulation to improve cognitive functioning in people with*  
2 *dementia*. Cochrane Database Syst Rev, 2012(2): p. Cd005562.
- 3 35. Lobbia, A., et al., *The efficacy of cognitive stimulation therapy (CST) for people with mild-to-*  
4 *moderate dementia: A review*. European Psychologist, 2019. **24**(3): p. 257-277.
- 5 36. Papanikolaou, Y., J.M. Jones, and V.L. Fulgoni, *Several grain dietary patterns are associated*  
6 *with better diet quality and improved shortfall nutrient intakes in US children and*  
7 *adolescents: A study focusing on the 2015–2020 Dietary Guidelines for Americans*. Nutrition  
8 Journal, 2017. **16**(1): p. 13.
- 9 37. Committee, U.S.D.G.A., *Dietary guidelines for Americans, 2010*. 2010: US Department of  
10 Health and Human Services, US Department of Agriculture.
- 11 38. Miller, E.R., 3rd, et al., *A dietary pattern that lowers oxidative stress increases antibodies to*  
12 *oxidized LDL: results from a randomized controlled feeding study*. Atherosclerosis, 2005.  
13 **183**(1): p. 175-82.
- 14 39. Gadgil, M.D., et al., *The effects of carbohydrate, unsaturated fat, and protein intake on*  
15 *measures of insulin sensitivity: results from the OmniHeart trial*. Diabetes Care, 2013. **36**(5):  
16 p. 1132-7.
- 17 40. Azadbakht, L., et al., *The Dietary Approaches to Stop Hypertension eating plan affects C-*  
18 *reactive protein, coagulation abnormalities, and hepatic function tests among type 2 diabetic*  
19 *patients*. J Nutr, 2011. **141**(6): p. 1083-8.
- 20 41. de Jager, C.A., et al., *Cognitive and clinical outcomes of homocysteine-lowering B-vitamin*  
21 *treatment in mild cognitive impairment: a randomized controlled trial*. Int J Geriatr  
22 Psychiatry, 2012. **27**(6): p. 592-600.
- 23 42. Lee, L.K., et al., *Docosahexaenoic acid-concentrated fish oil supplementation in subjects with*  
24 *mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled*  
25 *trial*. Psychopharmacology (Berl), 2013. **225**(3): p. 605-12.
- 26 43. Bo, Y., et al., *The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive*  
27 *Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized*  
28 *Controlled Trial*. Nutrients, 2017. **9**(1): p. 54.
- 29 44. Zhang, Y.P., et al., *Effects of DHA Supplementation on Hippocampal Volume and Cognitive*  
30 *Function in Older Adults with Mild Cognitive Impairment: A 12-Month Randomized, Double-*  
31 *Blind, Placebo-Controlled Trial*. J Alzheimers Dis, 2017. **55**(2): p. 497-507.
- 32 45. Desideri, G., et al., *Benefits in cognitive function, blood pressure, and insulin resistance*  
33 *through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: the*  
34 *Cocoa, Cognition, and Aging (CoCoA) study*. Hypertension, 2012. **60**(3): p. 794-801.
- 35 46. Dysken, M.W., et al., *Effect of vitamin E and memantine on functional decline in Alzheimer*  
36 *disease: the TEAM-AD VA cooperative randomized trial*. Jama, 2014. **311**(1): p. 33-44.
- 37 47. Sano, M., et al., *A controlled trial of selegiline, alpha-tocopherol, or both as treatment for*  
38 *Alzheimer's disease. The Alzheimer's Disease Cooperative Study*. N Engl J Med, 1997. **336**(17):  
39 p. 1216-22.

- 1 48. Garber, C.E., et al., *Quantity and quality of exercise for developing and maintaining*  
2 *cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults:*  
3 *guidance for prescribing exercise.* *Medicine & Science in Sports & Exercise*, 2011. **43**(7): p.  
4 1334-1359.
- 5 49. Zheng, G., et al., *Aerobic exercise ameliorates cognitive function in older adults with mild*  
6 *cognitive impairment: a systematic review and meta-analysis of randomised controlled trials.*  
7 *British journal of sports medicine*, 2016. **50**(23): p. 1443-1450.
- 8 50. Song, D., et al., *The effectiveness of physical exercise on cognitive and psychological*  
9 *outcomes in individuals with mild cognitive impairment: A systematic review and meta-*  
10 *analysis.* *International journal of nursing studies*, 2018. **79**: p. 155-164.
- 11 51. Ströhle, A., et al., *Drug and exercise treatment of Alzheimer disease and mild cognitive*  
12 *impairment: a systematic review and meta-analysis of effects on cognition in randomized*  
13 *controlled trials.* *The American Journal of Geriatric Psychiatry*, 2015. **23**(12): p. 1234-1249.
- 14 52. Association, A.P., *Diagnostic and statistical manual of mental disorders (DSM-5®)*. 2013:  
15 American Psychiatric Pub.
- 16 53. Medicine, A.A.o.S., *International Classification of Sleep Disorders*. 3rd ed ed, ed. A.A.o.S.  
17 Medicine. 2014.
- 18 54. Geiger-Brown, J.M., et al., *Cognitive behavioral therapy in persons with comorbid insomnia:*  
19 *A meta-analysis.* *Sleep Med Rev*, 2015. **23**: p. 54-67.
- 20 55. Irwin, M.R., J.C. Cole, and P.M. Nicassio, *Comparative meta-analysis of behavioral*  
21 *interventions for insomnia and their efficacy in middle-aged adults and in older adults 55+*  
22 *years of age.* *Health Psychol*, 2006. **25**(1): p. 3-14.
- 23 56. Trauer, J.M., et al., *Cognitive Behavioral Therapy for Chronic Insomnia: A Systematic Review*  
24 *and Meta-analysis.* *Ann Intern Med*, 2015. **163**(3): p. 191-204.
- 25 57. Cassidy-Eagle, E., et al., *Neuropsychological Functioning in Older Adults with Mild Cognitive*  
26 *Impairment and Insomnia Randomized to CBT-I or Control Group.* *Clin Gerontol*, 2018. **41**(2):  
27 p. 136-144.
- 28 58. Cassidy-Eagle, E., et al., *Cognitive behavioral treatment for insomnia in older adults with mild*  
29 *cognitive impairment in independent living facilities: A pilot study.* *Journal of Sleep Disorders*  
30 *and Medical Care*, 2018. **1**(1): p. 1-6.
- 31 59. de Oliveira, A.M., et al., *An intervention to reduce neuropsychiatric symptoms and caregiver*  
32 *burden in dementia: Preliminary results from a randomized trial of the tailored activity*  
33 *program-outpatient version.* *Int J Geriatr Psychiatry*, 2018.
- 34 60. McCurry, S.M., et al., *Increasing walking and bright light exposure to improve sleep in*  
35 *community-dwelling persons with Alzheimer's disease: results of a randomized, controlled*  
36 *trial.* *J Am Geriatr Soc*, 2011. **59**(8): p. 1393-402.
- 37 61. Naismith, S.L. and L. Mowszowski, *Sleep disturbance in mild cognitive impairment: a*  
38 *systematic review of recent findings.* *Curr Opin Psychiatry*, 2018. **31**(2): p. 153-159.

- 1 62. Richards, K.C., et al., *Strength training, walking, and social activity improve sleep in nursing*  
2 *home and assisted living residents: randomized controlled trial*. J Am Geriatr Soc, 2011.  
3 **59**(2): p. 214-23.
- 4 63. Lutz, A., et al., *Attention regulation and monitoring in meditation*. Trends in cognitive  
5 sciences, 2008. **12**(4): p. 163-169.
- 6 64. Lutz, A., et al., *Investigating the phenomenological matrix of mindfulness-related practices*  
7 *from a neurocognitive perspective*. American Psychologist, 2015. **70**(7): p. 632.
- 8 65. Malinowski, P. and L. Shalamanova, *Meditation and Cognitive Ageing: the Role of*  
9 *Mindfulness Meditation in Building Cognitive Reserve*. Journal of Cognitive Enhancement,  
10 2017. **1**(2): p. 96-106.
- 11 66. Luders, E. and N. Cherbuin, *Searching for the philosopher's stone: promising links between*  
12 *meditation and brain preservation*. Annals of the New York Academy of Sciences, 2016.  
13 **1373**(1): p. 38-44.
- 14 67. Larouche, E., C. Hudon, and S. Goulet, *Potential benefits of mindfulness-based interventions*  
15 *in mild cognitive impairment and Alzheimer's disease: An interdisciplinary perspective*.  
16 Behavioural Brain Research, 2015. **276**: p. 199-212.
- 17 68. Klimecki, O., et al., *The impact of meditation on healthy ageing – the current state of*  
18 *knowledge and a roadmap to future directions*. Current Opinion in Psychology, 2019. **28**.
- 19 69. Kurth, F., N. Cherbuin, and E. Luders, *Reduced age-related degeneration of the hippocampal*  
20 *subiculum in long-term meditators*. Psychiatry Research: Neuroimaging, 2015. **232**(3): p. 214-  
21 218.
- 22 70. Epel, E., et al., *Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and*  
23 *telomeres*. Annals of the New York Academy of Sciences, 2009. **1172**: p. 34-53.
- 24 71. Lenze, E.J., et al., *Mindfulness-Based Stress Reduction for older adults with worry symptoms*  
25 *and co-occurring cognitive dysfunction*. International journal of geriatric psychiatry, 2014.  
26 **29**(10): p. 991-1000.
- 27 72. Smart, C.M., et al., *Mindfulness Training for Older Adults with Subjective Cognitive Decline:*  
28 *Results from a Pilot Randomized Controlled Trial*. Journal of Alzheimer's Disease, 2016. **52**(2):  
29 p. 757-774.
- 30 73. Innes, K.E., et al., *Effects of Meditation versus Music Listening on Perceived Stress, Mood,*  
31 *Sleep, and Quality of Life in Adults with Early Memory Loss: A Pilot Randomized Controlled*  
32 *Trial*. Journal of Alzheimer's disease : JAD, 2016. **52**(4): p. 1277-1298.
- 33 74. Paller, K.A., et al., *Benefits of Mindfulness Training for Patients with Progressive Cognitive*  
34 *Decline and their Caregivers*. American journal of Alzheimer's disease and other dementias,  
35 2015. **30**(3): p. 257-267.
- 36 75. Woods, B., et al., *Reminiscence therapy for dementia*. status and date: Edited (no change to  
37 conclusions), published in, 2005.
- 38 76. O'Philbin, L., et al., *Reminiscence therapy for dementia: an abridged Cochrane systematic*  
39 *review of the evidence from randomized controlled trials*. Expert review of  
40 neurotherapeutics, 2018. **18**: p. 715-727.

- 1 77. Park, K., et al., *A systematic review and meta-analysis on the effect of reminiscence therapy*  
2 *for people with dementia*. International psychogeriatrics, 2019. **31**: p. 1581-1597.
- 3 78. Elfrink, T.R., et al., *Life story books for people with dementia: a systematic review*.  
4 International psychogeriatrics, 2018. **30**: p. 1797-1811.
- 5 79. Yen, H.-Y. and L.-J. Lin, *A systematic review of reminiscence therapy for older adults in*  
6 *Taiwan*. Journal of nursing research, 2018. **26**: p. 138-150.
- 7 80. Allen, A.P., et al., *Autobiographical memory, the ageing brain and mechanisms of*  
8 *psychological interventions*. Ageing research reviews, 2018. **42**: p. 100-111.
- 9 81. Woods, B., et al., *Reminiscence therapy for dementia*. Cochrane database of systematic  
10 reviews, 2018.
- 11 82. van der Steen, J.T., et al., *Music-based therapeutic interventions for people with dementia*.  
12 Cochrane Database of Systematic Reviews, 2018(7).
- 13 83. Abraham, I., et al., *Systematic review of systematic reviews of nonpharmacological*  
14 *interventions to treat behavioural disturbances in older patients with dementia*. *The*  
15 *SENATOR-OnTop series*. BMJ Open, 2017. **7**(3).
- 16 84. Pedersen, S.K.A., et al., *Effects of music on agitation in dementia: A meta-analysis*. Frontiers  
17 in Psychology, 2017. **8**(742).
- 18 85. Tsoi, K.K., et al., *Receptive music therapy is more effective than interactive music therapy to*  
19 *relieve behavioral and psychological symptoms of dementia: A systematic review and meta-*  
20 *analysis*. Journal of the American Medical Directors Association, 2018. **19**(7): p. 568-576.
- 21 86. Paul, D.R., et al., *Quality of communication life scale: Manual*. 2004.
- 22 87. Behrman, S., L. Chouliaras, and K.P. Ebmeier, *Considering the senses in the diagnosis and*  
23 *management of dementia*. Maturitas, 2014. **77**: p. 305-310.
- 24 88. Kovach, C.R., *Sensoristaxis and imbalance in persons with dementia*. Journal of Nursing  
25 Scholarship, 2000. **32**: p. 379-384.
- 26 89. Chung, J.C.C. and C.K.Y. Lai, *Snoezelen for dementia*. Cochrane Database of Systematic  
27 Reviews, 2002.
- 28 90. Strøm, B.S., S. Ytrehus, and E.K. Grov, *Sensory stimulation for persons with dementia: a*  
29 *review of the literature*. Journal of clinical nursing, 2016. **25**: p. 1805-1834.
- 30 91. Strøm, B.S., et al., *Effect of the sonas programme on communication in people with*  
31 *dementia: a randomized controlled trial*. Dementia and geriatric cognitive disorders extra,  
32 2017. **7**: p. 122-135.
- 33 92. Lorusso, L.N. and S.J. Bosch, *Impact of multisensory environments on behavior for people*  
34 *with dementia: a systematic literature review*. The Gerontologist, 2018. **58**: p. e168-e179.
- 35 93. Gonzalez, M.T. and M. Kirkevold, *Benefits of sensory garden and horticultural activities in*  
36 *dementia care: a modified scoping review*. Journal of Clinical Nursing, 2014. **23**: p. 2698-  
37 2715.
- 38 94. Chang, Y.-S., et al., *The efficacy of music therapy for people with dementia: A meta-analysis*  
39 *of randomised controlled trials*. Journal of Clinical Nursing, 2015(23-24): p. 3425.

- 1 95. Therapists, W.F.o.O., *Statement on Occupational Therapy 2012*. 2010, World Federation of  
2 Occupational Therapists.
- 3 96. Law, M., et al., *The person-environment-occupation model: A transactive approach to*  
4 *occupational performance*. Canadian journal of occupational therapy, 1996. **63**(1): p. 9-23.
- 5 97. Bennett, S., et al., *Occupational therapy for people with dementia and their family carers*  
6 *provided at home: a systematic review and meta-analysis*. BMJ Open, 2019. **9**(11): p.  
7 e026308.
- 8 98. Hsu, W.-Y., et al., *Effects of noninvasive brain stimulation on cognitive function in healthy*  
9 *aging and Alzheimer's disease: a systematic review and meta-analysis*. Neurobiology of  
10 aging, 2015. **36**: p. 2348-2359.
- 11 99. Inagawa, T., et al., *A meta-analysis of the effect of multisession transcranial direct current*  
12 *stimulation on cognition in dementia and mild cognitive impairment*. Clinical EEG and  
13 neuroscience, 2019. **50**: p. 273-282.
- 14 100. Wolinsky, F.D., et al., *Interim analyses from a randomised controlled trial to improve visual*  
15 *processing speed in older adults: the Iowa Healthy and Active Minds Study*. BMJ open, 2011.  
16 **1**: p. e000225.
- 17 101. Lampit, A., H. Hallock, and M. Valenzuela, *Computerized cognitive training in cognitively*  
18 *healthy older adults: a systematic review and meta-analysis of effect modifiers*. PLoS  
19 medicine, 2014. **11**.
- 20 102. Dodge, H.H., et al., *Use of high-frequency in-home monitoring data may reduce sample sizes*  
21 *needed in clinical trials*. PLoS One, 2015. **10**.
- 22 103. Moher, D., et al., *The CONSORT statement: revised recommendations for improving the*  
23 *quality of reports of parallel-group randomized trials*. Jama, 2001. **285**(15): p. 1987-1991.
- 24 104. Montgomery, P., et al., *Protocol for CONSORT-SPI: an extension for social and psychological*  
25 *interventions*. Implementation Science, 2013. **8**(1): p. 99.
- 26 105. Schulz, K.F., D.G. Altman, and D. Moher, *CONSORT 2010 statement: updated guidelines for*  
27 *reporting parallel group randomised trials*. BMC medicine, 2010. **8**(1): p. 18.
- 28 106. Nosek, B.A., et al., *Promoting an open research culture*. Science, 2015. **348**(6242): p. 1422-  
29 1425.
- 30 107. Rosenberg, A., et al., *Multidomain lifestyle intervention benefits a large elderly population at*  
31 *risk for cognitive decline and dementia regardless of baseline characteristics: The FINGER*  
32 *trial*. Alzheimer's & Dementia, 2018. **14**(3): p. 263-270.
- 33 108. Morris, M.C., et al., *MIND diet associated with reduced incidence of Alzheimer's disease*.  
34 Alzheimer's & Dementia, 2015. **11**(9): p. 1007-1014.

Figure 1: overview of Cochrane reviews on NPTs

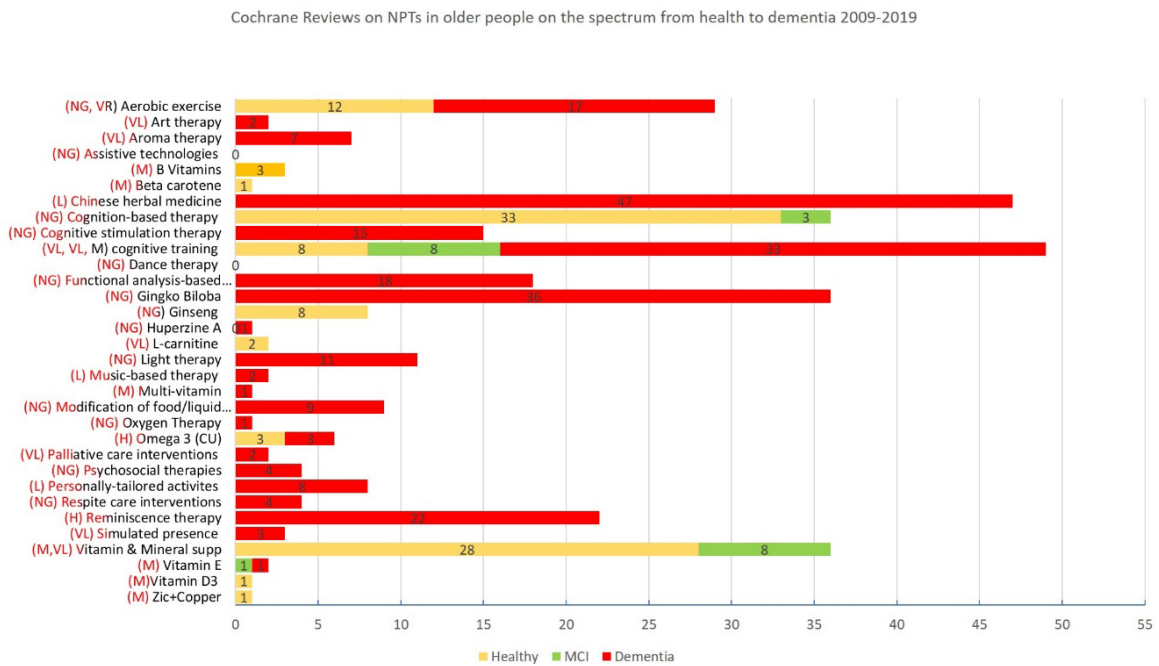


Figure 2: The tripartite structure of treatment theory. Source: Hart et al. 2019

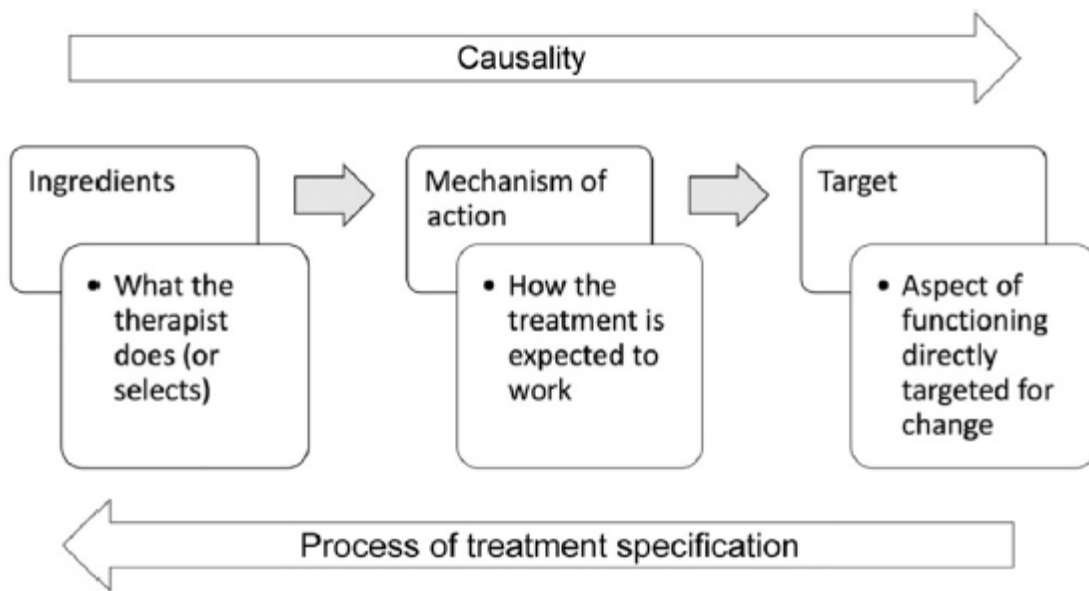


Figure 3. Timeline of the NPI-PIA Position Paper Project



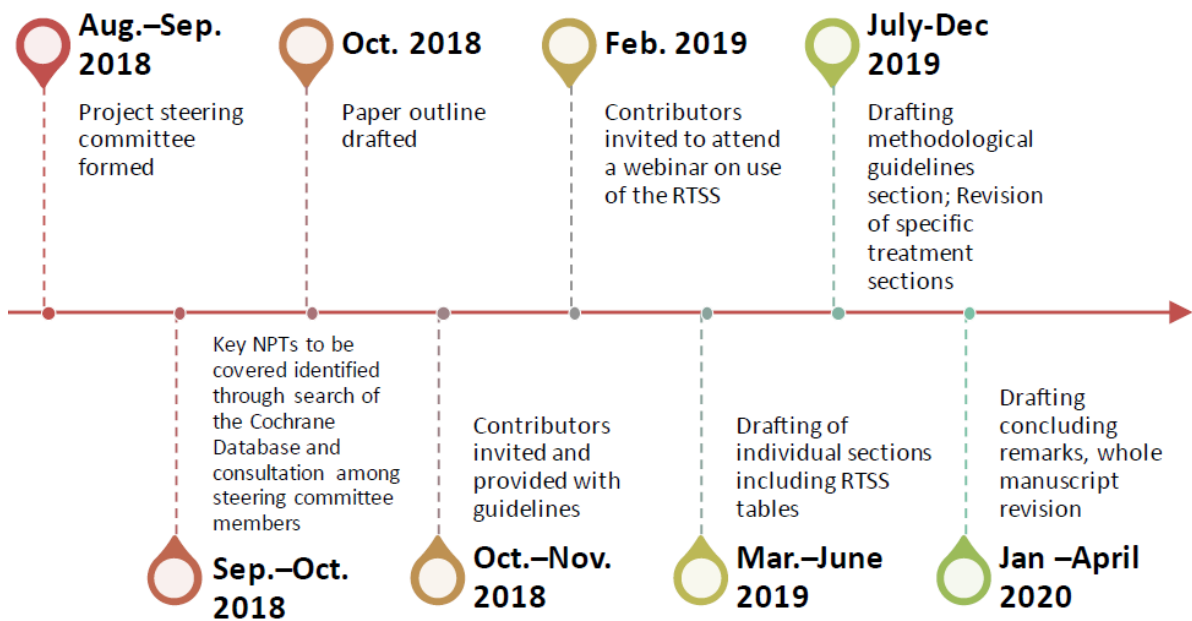


Figure 4: Overview of methodological considerations in the design of non-pharmacological treatments

