Non-Pharmacologic Interventions for Older Adults with Subjective Cognitive Decline:

Systematic Review, Meta-Analysis, and Preliminary Recommendations

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Abstract

In subjective cognitive decline (SCD), older adults present with concerns about self-perceived cognitive decline but are found to have clinically normal function. However, a significant proportion of those adults are subsequently found to develop mild cognitive impairment, Alzheimer's dementia or other neurocognitive disorder. In other cases, SCD may be associated with mood, personality, and physical health concerns. Regardless of etiology, adults with SCD may benefit from interventions that could enhance current function or slow incipient cognitive decline. The objective of this systematic review and meta-analysis, conducted in accordance with the PRISMA guidelines, is to examine the benefits of non-pharmacologic intervention (NPI) in persons with SCD. Inclusion criteria were studies of adults aged 55 + with SCD defined using published criteria, receiving NPI or any control condition, with cognitive, behavioural, or psychological outcomes in controlled trails. Published empirical studies were obtained through a standardized search of CINAHL Complete, Cochrane Central Register of Controlled Trials, MEDLINE with Full Text, PsycINFO, and PsycARTICLES, supplemented by a manual retrieval of relevant articles. Study quality and bias was determined using PEDro. Nine studies were included in the review and meta-analysis. A wide range of study quality was observed. Overall, a small effect size was found on cognitive outcomes, greater for cognitive versus

other intervention types. The available evidence suggests that NPI may benefit current cognitive function in persons with SCD. Recommendations are provided to improve future trials of NPI in SCD.

Keywords: mild cognitive impairment; Alzheimer's disease; complementary therapies; cognitive interventions; treatment outcome.

Introduction

In 2015 approximately 46.8 million people worldwide were living with dementia, and this number is expected to almost double every 20 years, reaching 74.7 million in 2030 (World Alzheimer Report, 2015). The total estimated worldwide cost of dementia in 2015 was US$818 billion (Alzheimer's Disease International, 2015). Alzheimer's disease (AD) remains the most common cause of dementia (Alzheimer's Association, 2016); as such, significant research and clinical efforts have been directed toward finding disease-modifying agents to slow or delay the rate of progression from normal cognitive aging to dementia. Despite these efforts, to date, there is no intervention known to cure or even reliably affect the course of AD.

Subjective cognitive decline (SCD) has been recently identified as a condition whereby apparently healthy older adults report concerns about a decline in cognitive function, but perform on cognitive tests within normal limits and have preserved instrumental activities of daily living (IADLs) (Jessen et al., 2014). Historically, many older adults with SCD may have been regarded by healthcare professionals as the "worried well"; indeed, subjective complaints about cognition are often associated with mood and personality factors, as well as chronic health impairments (Boone, 2009; Cargin, Collie, Masters, & Maruff, 2008; Comijs, Deeg, Dik, Twist, & Jonker, 2002; Kliegel & Zimprich, 2005). However, emerging evidence from longitudinal aging studies indicate that adults with SCD are more likely than their healthy peers to present with AD biomarkers such as neurodegeneration (Meiberth et al., 2015; Perrotin et al., 2015; Peter et al., 2014; Saykin et al., 2006) and amyloid burden (Amariglio et al. 2012; Perrotin et al. 2012; Snitz et al. 2015a). This suggests that, for some older adults, SCD may represent a preclinical phase of AD.

Given the rapidly increasing aging population, research is beginning to move away from an exclusive focus on treatment of dementia toward early detection of persons in the preclinical stage, the purpose of which being to institute prevention-interventions before significant clinical symptoms are manifest (Imtiaz, Tolppanen, Kivipelto, & Soininen, 2014). Pharmacologic interventions are a topic of great interest in persons with already manifest cognitive decline, including mild cognitive impairment (MCI) and AD, and continue to be pursued in earnest. However, given the heterogeneity of etiology and presentation of SCD (Jessen et al., 2014), it is difficult to speculate about a focal target for pharmacologic intervention, particularly if individuals have minimal manifest clinical symptoms. Even in populations with documented cognitive impairment, the evidence is mixed as to the positive impact of medication use in improving cognitive and behavioral function (Fitzpatrick-Lewis, Warren, Ali, Sherifali, & Raina, 2015; Tan, Yu, Wang, & Tan, 2014). In addition, existing medications often have significant side effects, and in some cases may be directly contraindicated in certain individuals such as those with specific medical comorbidities (Winslow, Onysko, Stob, & Hazlewood, 2011).

Non-pharmacologic intervention (NPI) could be a viable alternative for persons with SCD. Although there is a paucity of formal economic analyses of NPI in older adults (Davis et al., 2015), one can theorize that these are likely to be less expensive to develop and implement than pharmacologic interventions, and have minimal, if any side effects, even when ineffective. Moreover, unlike medications that must be prescribed by physicians, NPI, once standardized, can be implemented by a variety of healthcare personnel who have the relevant training and expertise (e.g., Master's level clinicians such as speech-language pathologists or occupational therapists, as well as clinical psychologists). Perhaps more importantly, persons with SCD are presumed to have relatively preserved current cognitive function and greater access to cognitive reserve

(Stern, 2009; 2012), both of which improve the likelihood of their being able to benefit from NPI before significant cognitive difficulties are manifest.

Regardless of the specific etiology, many adults with SCD may benefit from early intervention using NPI. For those with biomarkers associated with preclinical AD but no clinical symptoms, such interventions could slow or delay the onset of pathologic cognitive decline. Recent evidence indicates that training-induced neuroplasticity can continue into older adulthood, suggesting that certain NPI could improve the underlying structure and function of the brain (Greenwood & Parasuraman, 2010; Jellinger & Attems, 2013). Mechanistically, at this very early stage of decline, it is presumed that individuals have sufficiently intact cognitive function that could be harnessed toward either restitution or enhancement of specific cognitive processes such as attention, or compensation for subtle deficits in systems such as memory (Sohlberg & Mateer, 2001). Conversely, for those for whom SCD is driven by mood, personality, and physical health concerns, evidence suggests that variables such as depression (Da Silva et al., 2013; Diniz et al., 2013) and neuroticism (Duberstein et al., 2011; Low et al., 2013) can independently predict decline to MCI and dementia. Concerted efforts at early intervention in these subsamples could produce concurrent improvements in cognitive function and psychological health and well being, in addition to possibly attenuating the risk for future non-normal cognitive decline.

Two prior systematic reviews have been conducted on interventions for persons with cognitive complaints. Metternich and colleagues (2010) conducted a meta-analysis of fourteen randomized controlled trials (RCTs) of any NPI for individuals with subjective memory complaints. Cognitive restructuring was found to reduce self-reported memory complaints, while only memory training improved objective memory function. The specific meaning of these

results for persons with SCD is unclear; a review of the individual studies included indicate that several studies provided incomplete information on baseline screening of participants, raising concern about the inclusion of either healthy older adults or persons with MCI. More recently, Canevelli and colleagues (2013) reviewed six studies using cognitive training interventions for individuals with subjective cognitive complaints. While each study reported some improvement in cognitive function in their samples, the studies varied widely in terms of characteristics and feasibility of implementation. Although this review did focus specifically on persons with SCD broadly defined, the authors included clinical trials of any NPI, not specifying whether they limited their review to RCTs or even controlled trials of any kind, raising questions about the rigor of the studies on which their conclusions were based. Neither of these reviews specified an age range for participants or noted that studies were confined to older adults.

Objectives of the Current Study

SCD has emerged relatively recently in research. As a consequence, the topic of interventions in this population has been relatively unexplored. Evidence from prior meta-analyses is unclear as to whether the benefits of NPI apply directly to persons with SCD as opposed to healthy older adults in general. Moreover, the current research base includes sources other than controlled trials. Therefore, the primary objective of the current study was to evaluate the benefits of NPI (cognitive, behavioral, psychosocial, and complementary/ alternative medicine) on cognitive, behavioral, and psychological functioning in persons aged 55+ with SCD in the context of controlled trials with any kind of control condition. A secondary objective was to provide preliminary theoretical and research recommendations for future clinical trials of NPI in this population, thereby contributing to the further development of research and intervention evidence base in SCD. Given the very recent standardization of SCD criteria (Jessen

et al., 2014), a broad definition of SCD was adopted along with general eligibility criteria for intervention and study design to include as many studies as possible in this nascent field.

Methods

This systematic review and meta-analysis followed recommendations provided for conducting and publishing meta-analyses in neuropsychology (Gates & March, 2016) and aligns with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher, Liberati, Tetzlaff, Altman, and the PRISMA Group, 2009).

Literature Search

Six of the study authors (*masked for double-blind review*) provided keywords for the literature search. Selection of keywords was determined for: (1) participant subjective cognitive decline; (2) intervention type [(a) cognitive interventions, (b) psychosocial interventions, (c) physical interventions, and (d) complementary and alternative medicine]; (3) outcomes [(a) cognitive, (b) behavioral, (c) self-report]; and (4) study design. The final list of keywords was obtained by consensus by the aforementioned authors. The search of CINAHL Complete, Cochrane Central Register of Controlled Trials, MEDLINE with Full Text, PsycINFO, and PsycARTICLES, performed during November 2015 with no date restrictions specified, was initially executed by the first author, and then independently run by two other authors to promote reliability. A list of all exact search terms included in the protocol along with search limits applied for each database is provided in supplementary materials.

Eligibility criteria were: (1) a controlled trial of (2) an NPI targeted at improving cognitive, behavioral or psychological functioning among (3) participants 55 years or older with (4) a diagnosis of SCD or a conceptually equivalent diagnosis. Authors used the Jessen et al.

(2014) criteria to adjudicate whether participants did or did not meet criteria for SCD. There is, as of yet, no gold standard for how to operationalize these criteria. For the purposes of the current study, we interpreted the criteria based on the following: participants being clinically normal based on objective assessment, self (and where possible, informant)-reported complaints or concern about cognitive impairment or decline, and any perceived cognitive decline could not be better accounted for by a major medical, neurologic, or psychiatric diagnosis. In order to be included into meta-analysis, eligible studies needed to report, or provide via email correspondence, (5) sufficient data for inclusion in meta-analysis (i.e., group sample sizes, pre-test means/SDs, and post-test means/SDs or mean change). The studies needed to (6) be published in an academic book or peer-reviewed journal, and (7) be written in the English language. The quality rating (i.e., PEDro scale; Maher, Sherrington, Herbert, Moseley, & Elkins, 2003) for each study provided a proximal assessment for the risk of individual study bias.

Statistical Analysis

For the meta-analyses, effect sizes were calculated using standardized methods. Full equation models are provided in supplementary materials. Publication bias was considered as part of the meta-analytic approach.

Results

Systematic Review

After screening for duplication and elimination of ineligible studies (e.g., younger adults with chemotherapy-related cognitive impairment), 16 were deemed appropriate for initial inclusion. These articles were supplemented by manual retrieval of articles from five prior systematic reviews and meta-analyses (Canevelli et al., 2013; Floyd & Scogin, 1997; Gross et al., 2012; Metternich et al., 2010; Wilson, 2005), as well as published manuscripts known to any

of the authors that did not emerge in the search protocol. The automated and manual search protocols resulted in a combined total of 38 articles to be considered for inclusion. Each of these articles was assigned to two raters who independently adjudicated the appropriateness of each article for inclusion. In particular, we excluded any studies where the classification method of participants was unclear (e.g., intermixing of persons with SCD with healthy older adults or those with MCI). Where a discrepancy occurred in the rating for inclusion (in 4/38 cases), a third rater evaluated the discrepancy and made a final decision. Figure 1 provides a flow diagram of the search process; a list of references for articles identified by the search, but not ultimately considered in the meta-analysis, is provided in the supplementary materials. Each included article was assigned to two raters who independently extracted the necessary data for analysis, using a standardized protocol and extraction spreadsheet created by the first two authors.

This resulted in a total of 11 articles eligible for inclusion in the final systematic review. Given insufficient data across studies on self-report outcomes, a decision was made to run the meta-analysis only on the cognitive outcomes, where cognition was taken as a global outcome. Given the small number of studies included, it was not possible to look at treatment moderators (e.g., age, gender), and therefore the analysis was limited to an overall estimate of effect for cognitive outcomes across intervention types. Three of the articles did not contain complete cognitive data (Andrewes et al., 1996; Smart et al., 2016; van Hooren et al., 2007). Of these three, necessary data were obtained from only one set of authors (i.e., Smart et al., 2016). This resulted in a final total of 9 articles being included in the meta-analysis on cognitive outcomes of NPI studies on SCD.

The 9 eligible studies provided a pool of 378 participants in intervention conditions and 298 participants in control conditions (Table 1). The sample across studies varied

demographically in terms of mean age (range: 64.90 to 77.41), gender composition (% male range: 0 to 50.60), and ethnicity (% white range: 0 to 100). From the studies there were 13 intervention groups and 9 control groups. Cognitive interventions, broadly defined, were the most common NPI, found in 8/9 studies. One study (Lautenschlager et al., 2008) reported only an exercise intervention, while two studies (Barnes et al., 2013; Fabre et al., 1999) evaluated three separate forms of intervention (i.e., cognitive intervention, physical exercise, and combined cognitive/physical). The majority of interventions occurred in group settings, with the exception of one study reporting an individualized intervention (Lautenschlager et al., 2008). The interventions also varied in terms of length (i.e., 4 to 24 weeks), session duration (i.e., 45 minute to 2.5 hours) and frequency (range: 1 to 3 sessions per week).

The mean study quality was 6 points on the 10-point PEDro scale, ranging from 2 to 9 across studies. Notably, lower quality studies often produced larger effect sizes than higher quality ones, indicating that less rigorous research designs potentially overestimate treatment effects. However, there was little evidence of bias affecting the findings of this review. There were two potentially eligible studies that lacked the statistical data necessary for inclusion in the meta-analysis; the findings of Andrewes et al. (1996) were generally consistent with this meta-analysis, whereas Van Hooren et al. (2007) found improvements in self-report measures only and not objective cognitive function. This suggests that we did not unduly exclude studies with a radically different outcome than those contained in the final meta-analysis. Publication bias was incorporated into the meta-analysis and discussed below. Thus, we can be reasonably confident that our results are an accurate portrayal of the impact of NPI on cognitive function in older adults with SCD broadly defined.

Meta-Analysis

Two meta-analytic models were run using studies reporting cognitive outcomes. Outcomes were limited to the immediate post-intervention assessment, as only two studies included longitudinal follow-up data (i.e., Lautenschlager et al., 2008 and Tsai et al., 2008), which was insufficient to provide separate analyses of maintenance of intervention gains. The first model involved effect sizes for all NPI types reported by researchers (i.e., cognitive intervention, physical exercise, and combined cognitive/physical) and the second model involved effect sizes for solely cognitive interventions. For studies that evaluated multiple NPI with a single control group, an effect size was calculated for each intervention separately, using the same control condition. The data available from eligible studies ultimately yielded 8 effect sizes for cognitive intervention trials, 3 effect sizes for physical exercise trials, and 2 effect sizes for combined cognitive/physical trials. Table 2 provides the effect size estimates and highest density intervals (HDIs) for the study-level and overall effects for each meta-analysis. The HDI contains the highest 95% of the posterior, which indicates that there is a 95% chance that the true effect falls within its upper and lower bounds. These effect sizes are displayed graphically through forest plots in Figures 2 and 3. The overall effect for all NPI types came to 0.22 (HDI = .01 to .51) and the overall effect for cognitive intervention paradigms only came to 0.37 (HDI = 0.06 to 0.71). According to Cohen (1992), both of these effect sizes are deemed to be small. Figure 4 displays estimated weight functions $\omega(\theta)$ for the publication bias analysis for the cognitive and cognitive/physical models. Note that both curves are very flat, indicating minimal publication bias, which is to be expected with the publication of several studies with very small effect sizes.

Discussion

Summary of Current Findings

The results of our systematic review indicate significant diversity in SCD intervention trials to date, with cognitive interventions dominating the field. Meta-analyses indicate a small but significant effect of all NPI on cognitive outcomes in adults age 55 + with SCD, indicating that these interventions have immediate benefits on cognition. This finding is important as it demonstrates that cognitive enhancement is possible even when persons appear cognitively normal on standardized neuropsychological testing. Although the aggregate of all NPI demonstrated a small effect size, the effect was larger when cognitive interventions were analyzed alone. This speaks to the importance of specificity in matching treatment type, purported mechanism of action, and observed outcomes (Hart et al., 2014). This specificity of effects is consistent with the findings of the Metternich et al. (2010) review, which found that cognitive restructuring reduced subjective memory complaints, while memory training improved objective memory function.

The majority of studies (i.e., 7/9) only included short-term (immediate post-intervention) follow-up assessment. Therefore the extent to which interventions in SCD reliably slow or change the trajectory of any future cognitive decline remains unknown. However, in those two studies that did conduct longitudinal follow-up (i.e., Lautenschlager et al., 2008 and Tsai et al., 2008), gains in cognition appeared to be maintained over time. Moreover, due to the limited number of eligible studies, it was not possible to examine potential treatment moderators (e.g., age, ethnicity, duration of complaints/concern, etc.) beyond the separate analysis looking at cognitive interventions only. As the phenomenon of SCD becomes more widely recognized, and literature accumulates on this topic, it will be possible to gain a more nuanced understanding of which treatments work for which individuals under which circumstances, so that interventions can be tailored and targeted toward those who will benefit the most.

The current findings have immediate implications for individuals with SCD. Providing NPI as part of preventative care could empower individuals to take proactive steps in support of their own cognitive and emotional well-being, rather than having to wait until significant clinical symptoms are present. One such example of this type of work already being implemented is the FINGER study (Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability), a large-scale RCT designed to target diet, exercise and cognitive training in older adults with vascular risk factors. Preliminary results of this study suggest beneficial effects on cognition in at-risk individuals (Ngandu et al., 2015). Moreover, NPI, once administered, have minimal if any maintenance costs, as compared to medications, which require continual usage and monitoring and therefore ongoing costs to the individual, caregivers, and the healthcare system (Bond et al., 2012; Pouryamout et al., 2012). Therefore these findings have economic and public health implications in terms of provision of time and cost-effective interventions for a rapidly growing segment of the population who may need care.

As the population ages, we will be faced with increasing numbers of older adults experiencing both normal age-related cognitive decline as well as substantial numbers who may experience non-normal decline such as MCI and dementia (Alzheimer's Association, 2016). Identifying persons at the earliest stages of pathologic cognitive decline presents a unique opportunity for intervention efforts, particularly using NPI, before significant clinical symptoms are manifest. While a limited amount of novel studies have been conducted since the prior two systematic reviews by Metternich et al. (2010) and Canevelli et al. (2013), nevertheless the current study makes unique contributions to the literature, including (1) the exclusive focus on persons aged 55+ classified as having SCD commensurate with our current understanding of this phenomenon, and (2) the inclusion of only controlled trials of NPI.

Recommendations for Best Practices in Intervention Research in SCD

The primary goal of the current study was to produce an updated systematic review and meta-analysis. Research on SCD as a clinical entity is a relatively new endeavor, and as such we anticipated that interventions would likewise be fairly limited. There is a current focus in the field to rigorously define and characterize persons with SCD in an effort to harmonize across research studies (Jessen et al., 2014; Molinuevo et al., in press; Rabin et al., 2015). Likewise the field of cognitive interventions is mired by inconsistencies in terminology and characterization of treatment types and anticipated treatment effects (Hart et al., 2014). Precisely for that reason, in this review we intentionally chose the term "cognitive interventions" to be most inclusive of cognitive training, cognitive rehabilitation, and cognitive stimulation, all of which have different meanings but are frequently conflated in the older adult literature (Bahar-Fuchs, Clare, & Woods, 2013; Clare & Woods, 2004). In order to expeditiously move the field forward, a second goal of this study was to use the results of this systematic review and meta-analysis, as well as draw on existing theoretical knowledge, to provide preliminary recommendations and guidance for researchers wishing to conduct future clinical trials of NPIs in persons with SCD.

1. Operationalization of SCD classification in studies. Of all the reviewed studies rendered ineligible, a majority (n = 20) were excluded due to a lack of information on how the study samples were characterized with regards to presence/absence of SCD. This is perhaps unsurprising, given that many of the studies were published many years before SCD was discussed in the literature, or operationalized as a diagnostic entity (Jessen et al., 2014). At present, there is no gold standard approach to classification of persons with SCD, and even amongst the major research groups studying SCD, there is a diversity of approaches currently in use (Rabin et al., 2015). That said, the reader is referred to Jessen et al. (2014) and Molinuevo et

al. (in press) for guidance on how to best operationalize SCD criteria in individual research studies. Rather than striving for all studies to use exactly the same operationalization, to the extent that clinical trials include detailed information on exactly how participants are classified, this will allow for more appropriate aggregation of results across different studies.

2. Participant characterization. Several of the studies we reviewed were deemed ineligible due to the lack of information provided with regards to the baseline cognitive function of participants. This raised concerns that some participants may have, in fact, been classifiable as MCI. Aside from the obvious diagnostic utility, adequate characterization of participants is critical to ascertain whether there are potential moderators of treatment effects, such as age, gender, premorbid function, etc. To address this issue, in future studies we minimally recommend inclusion of an estimate of premorbid function, in addition to a broad neuropsychological screen of attention, memory, language, and executive functions. Many older adult studies focus almost exclusively on memory, but the advent of the Jessen et al. (2014) criteria, and the use of "cognitive" rather than "memory" in the term SCD, respect the fact that an individual's main complaints – and underlying impairment – may not be limited to memory.

Although many of these measures are already used in existing longitudinal studies, it is not uncommon for analyses to be based on raw scores only. While raw scores can be useful to measure group-level phenomena, they do not provide clinically useful information for the interpretation of individual participant scores (i.e., whether there is evidence of clinical impairment at the individual level). Additionally, there is some evidence that SCD is associated with greater risk of cognitive decline in persons with higher versus lower education (Jonker et al., 2000, van Oijen et al., 2007). As such, we strongly recommend that neuropsychological measures be scored with respect to age and, where possible, education-based norms, in order to

corroborate of the SCD criterion of no clinical-neuropsychological impairment (Jessen et al., 2014), provide an estimate of cognitive reserve, and shed light on how baseline cognitive function may moderate response to intervention.

Given the possible inter-relationships between mood, anxiety, cognitive complaints, and objective cognition, we also recommend inclusion of screening measures of psychological functioning. Baseline scores on these measures could function as moderators of intervention response, while repeat administration post-intervention could serve as important outcome variables. It is acknowledged that large-cohort population-based studies – many of which are used to investigate SCD – likely have limited time and resources for in-depth characterization of every participant compared to clinic or volunteer samples. In the context of such large-scale studies, one strategy could be to recruit smaller subsamples as specific targets for intervention that will allow for more detailed participant characterization.

3. Sample size as a function of research design. Intervention trials, particularly NPI, require significant resources to complete in a rigorous fashion. Researchers must consider this in the context of estimating a necessary sample size to produce a robust treatment effect. In choosing an intervention modality and anticipating the required sample size, several factors warrant consideration:

(a) Scalability of the intervention. Certain interventions could be offered on a large scale with minimal input from trained interventionists, such as those disseminated via the Internet. In contrast, other interventions require more in-depth, face-to-face contact with participants (either individually or in groups), and have higher burdens for maintenance of treatment fidelity, such as mindfulness training (Smart et al., 2016). To maintain the integrity of these modalities, the latter type of interventions will necessarily be conducted in smaller sample sizes. While small samples

are often considered a limitation, this can be circumvented through several avenues, including multi-modal assessment of treatment effects using sensitive measures (see further discussion below), as well as multiple assessment points. For example, studies using measurement burst designs (Nesselroade, 1991) have many benefits in the context of aging research. Specifically, burst designs with three or more measurement points have a greater tolerance for smaller sample sizes due to the reliability of information gained from intensive within-person measurements. Moreover, such designs allow for the ascertainment of how behavioral and biological processes unfold over different periods of time (Rast, MacDonald, & Hofer, 2012), as well as the temporal dynamics and mutual influences of cognitive, behavioral, emotional, and neural processes (Sliwinski, 2008). Finally, researchers should compute necessary sample sizes based on available effect sizes for the intervention of interest. In the current study, the overall effect of NPIs on cognitive outcomes is estimated as small (0.22 for all NPI; 0.37 for cognitive interventions specifically). However, depending on the intervention of interest, researchers are also advised to consult complementary bodies of literature in fields such as cognitive rehabilitation, psychotherapy, and health psychology where effect size information can be interpreted with consideration of different interventions and different outcomes (e.g., self-report as opposed to cognitive outcomes).

(b) N = 1 case series designs. Rigorously controlled $n = 1$ case series are a viable option for those who have limited access to resources to conduct large-scale studies, or are studying a population with a low base rate of occurrence in a given setting. An accumulation of case studies obtained in routine clinical practice can provide evidence for intervention *effectiveness*, which is a complementary form of evidence to the rigorously controlled RCTs used to provide proof of *efficacy* (Chambless & Hollon, 1998). According to the Chambless criteria for empirically

supported psychological treatments (Chambless et al., 1998), a case series of nine or greater is sufficient to meet the standard of Class I evidence in support of an intervention.

4. Measurement of response to intervention. It is not uncommon for intervention studies to use neuropsychometric measures as the main outcome of interest. While such measures can be valuable, there are several cautions against relying solely on these measures in intervention studies on SCD. First, by definition, persons with SCD score within normal limits on standardized clinical-neuropsychological tests. As such, ceiling effects may make it more difficult to ascertain response to intervention in this population as compared with individuals who already have clinically manifest impairment (e.g., persons with MCI). Second, one must be concerned that any pre/post improvements on neuropsychological tests that are observed could be due to practice effects given the likely short test-retest interval. Third, neuropsychometric tests imply an objective change in cognition (i.e., restitution of function), which may or may not be the primary objective of the intervention. That is, if the objective of the intervention is to improve compensatory strategy use and everyday behavior, then neuropsychometric tests are unlikely to be sensitive to this kind of change. (See the section on *Mechanism of Action* below for further discussion of this issue.)

If the intervention is specifically intended to provide restitution of function, and there is a desire to measure objective cognitive change, novel and challenging cognitive-experimental tasks, in conjunction with *in-vivo* measures of brain function (e.g., EEG/ERP, fMRI), may be a more sensitive alternative to neuropsychometric tests (Campanella, 2013; de Waal et al., 2014; Smart et al., 2016). If a decision is made to use clinical-neuropsychological tests, rather than using raw scores, researchers are advised to compute *reliable change indices* (RCIs) that consider practice effects in producing an estimate of clinically meaningful change as opposed to

statistically significant change (Duff, 2014; Frerichs & Tuokko, 2006). RCIs can also be calculated on many clinical self-report measures of mood and anxiety. It stands to reason that any standardized clinical test used should have adequate psychometric properties that are ideally established in an elderly population (e.g., Geriatric Depression Scale vs. the Beck Depression Inventory-II).

Dose-response relationship. Different cognitive and psychological constructs may require different durations of treatment to show meaningful improvement, and a lack of significant clinical effect may be due to suboptimal exposure to the treatment. The dose-response relationship can be challenging to ascertain in cognitive studies, given the various moderators of intervention response, including premorbid function as well as psychological variables such as intrinsic motivation. That said, researchers should examine relevant literature in fields such as cognitive rehabilitation, paying close attention to any recommendations on the dose for an existing intervention. In further support of this, researchers are encouraged to standardize and manualize novel interventions, so that other researchers can replicate them and an ideal dose be established.

Specifying mechanism of action. As noted previously, detecting significant effects from NPI in older adults in general is obfuscated by the imprecise and interchangeable use of terms such as cognitive training, cognitive rehabilitation, and cognitive stimulation. In addition, many intervention studies focus primarily on outcome measures without specifying *a priori* why a particular intervention would be theorized to specifically impact that measure or even what the presumed mechanism of action is for that treatment. The findings of the prior review by Metternich et al. (2010) demonstrate the specificity of intervention type to intervention outcomes in SCD. As such, the chances of detecting a significant effect will be greatly enhanced by clearly

specifying the intervention's presumed mechanism of action *a priori*, as well as using measures expressly designed for the purpose of detecting change in this construct (Hampstead, Gillis, & Stringer, 2013). It is important to reiterate that not every intervention will necessarily produce measurable change in cognitive function, particularly if the purpose is compensation rather than restitution. Where the mechanism of action is compensation, then ecologically relevant outcomes are likely to be more revealing than measures of cognition or brain function. The reader is referred to Hart et al. (2014) who propose a taxonomic model of rehabilitation interventions that consider the various levels of analysis by which an intervention's efficacy or effectiveness might be established.

Control conditions and duration of follow-up. As clinical trials can be both time and resource-intensive, many studies may opt to employ a waitlist control condition. However, this may create an expectancy effect in the control group, obfuscating the true impact of the intervention. As such, researchers are advised where possible to use either (1) a passive control, such as treatment-as-usual, or (2) an active control matched with the intervention on many or most of its major characteristics except for the presumed active ingredient.

Many trials aim to answer the question of whether NPI has a preventative effect on future cognitive decline, yet only assess outcomes immediately post-intervention, something that was borne out by the current review. Longitudinal follow-up (i.e., at least 1-year post, or longer) is necessary for several reasons. For one, research indicates that training-induced neuroplasticity may occur on longer time-scales in older as compared to younger adults (Jellinger & Attems, 2013). Moreover, because persons with SCD are by definition within normal limits on clinical-neuropsychological tests and are functionally independent, positive intervention effects may not be observed until months or even years later. Both of these points are illustrated by findings from

the ACTIVE trial, a large-scale, multi-center RCT of cognitive training in healthy older adults. This study has found that protective effects on IADLs were most pronounced at the 3 to 5-year follow-up, and further maintained at 10-year follow-up (Rebok et al., 2014). In other words, what might appear to be a "null result" immediately following intervention could actually be a positive result over time. It is understood that longitudinal studies are time and resource-intensive; however, it behooves researchers to make the case to funding agencies that such studies are necessary to truly answer the question of whether these interventions can slow or delay future cognitive decline. The current review provides proof of principle for short-term training benefits in persons with SCD that can be used in support of seeking funding for longer-term studies.

Conclusions

In summary, the current systematic review and meta-analysis indicates that NPI can be effectively implemented in populations with SCD, and in particular that cognitive interventions can benefit objective cognitive functioning. Given the potential for individuals with SCD to cognitively decline to diagnoses of MCI and dementia, the current findings are encouraging and suggest that implementation of NPI trials in this population is warranted. Conversely, even for individuals who will not decline to MCI and dementia, NPI may offset some normal age-related cognitive decline, thus potentially supporting productive aging, and enhancing quality of life and well-being.

NPI are likely to be more cost-effective than medications, associated with less, if any, side effects, and can be disseminated by a wide variety of appropriately trained and experienced health professionals. Our hope is that these findings, along with the preliminary recommendations provided, will inform clinical intervention and encourage further research in

this area to include trials with longitudinal follow-up that can address the question of whether such interventions impact upon or alter the trajectory of non-normal cognitive decline.

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Note: citations marked with an asterisk (*) were those included in the meta-analysis.

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Table 1. *Controlled NPI trials for SCD: Study Characteristics*

			Sample Characteristics				Treatment Characteristics		
Author	PEDro (Study Quality)	Condition	*N*	Mean Age	% Male	% White	Length (Wks.)	Session Length (Hrs)	Freq. (Sessions /week)
Barnes et al. (2013)	9	Combined	32	74.8	37.5	65.6	12	1	3
		Cognitive	31	73.8	41.9	71	12	1	3
		Exercise	31	71.1	32.3	54.8	12	1	3
		Active Control	32	73.9	37.5	68.8	12	1	3
Cohen-Mansfield et al. (2015)	5	Cognitive	15	72.8	40		10		
		WL Control	14	73.8	21.5		10		
Fabre et al. (1999)	6	Combined	8	64.9	12.5	100	8	2.5	3
		Cognitive	8	67.5	12.5	100	8	1.5	1
		Exercise	8	65.4	25	100	8	1	2
		Control*	8	65.7	12.5	100	8		
Fairchild & Scogin (2010)	5	Cognitive	28	73.45	17.86	85.71	6	.75	1
		Active Control	25	71.24	20	68.00	6	0.17	0.33
Hoogenhout et al. (2012)	7	Cognitive	24	66	0	100	4	1.5	2
		WL Control	26	66.1	0	100			
Kwok et al. (2013)	3	Cognitive	86	77.41	12.8	0	8	1	1
		Active Control	90	73.5	16.7	0	8		
Lautenschlager et al. (2008)	8	Exercise	85	68.7	48.2		24	0.833	3
		Active Control	85	68.6	50.6		24		
Smart et al. (2016)	9	Cognitive	8	69.6	26.67	91.7	8	2	1
		Active Control	7	69.6	26.67	91.7	5	2	1
Tsai et al. (2008)	2	Cognitive	14	69.4		0	5	2	2
		Active Control	11	69.4		0	8	1.5	1

Note: *Fabre et al. did not specify whether their control condition was active or waitlist (WL).

Table 2. *Effect Sizes of NPI for SCD*

Study	Condition	All Interventions Mean d_{ppc} (HDI)	Cognitive Only Mean (HDI)
Barnes et al.	Cognitive	0.02 (-0.14, 0.18)	0.03 (-0.14, 0.19)
Barnes et al.	Exercise	0.01 (-0.15, 0.17)	
Barnes et al.	Combined	0.02 (-0.13, 0.17)	
Cohen-Mansfield et al.	Cognitive	0.29 (-0.22, 0.85)	0.43 (-0.16, 1.03)
Fabre et al.	Cognitive	0.34 (-0.20, 0.99)	0.46 (-0.19, 1.14)
Fabre et al.	Exercise	0.30 (-0.27, 0.95)	
Fabre et al.	Combined	0.37 (-0.19, 1.02)	
Fairchild & Scogin	Cognitive	0.73 (0.02, 1.36)	0.88 (0.20, 1.44)
Hoogenhout et al.	Cognitive	0.12 (-0.30, 0.53)	0.19 (-0.27, 0.63)
Kwok et al.	Cognitive	0.39 (0.19, 0.57)	0.41 (0.22, 0.59)
Lautenschlager et al.	Exercise	-0.13 (-0.33, 0.08)	
Smart et al.	Cognitive	0.29 (-0.16, 0.79)	0.39 (-0.11, 0.91)
Tsai et al.	Cognitive	0.20 (-0.21, 0.64)	0.28 (-0.19, 0.71)
Overall		0.22 (0.01, 0.51)	0.37 (0.06, 0.71)