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Everyday Impact of Cognitive Interventions in Mild Cognitive Impairment: a Systematic Review and Meta-Analysis

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Abstract

Cognitive interventions in Mild Cognitive Impairment (MCI) seek to ameliorate cognitive symptoms in the condition. Cognitive interventions may or may not generalize beyond cognitive outcomes to everyday life. This systematic review and meta-analysis sought to assess the effect of cognitive interventions compared to a control group in MCI on generalizability outcome measures [activities of daily living (ADLs), mood, quality of life (QOL), and metacognition] rather than cognitive outcomes alone. PRISMA guidelines were followed. MEDLINE and PsychInfo were utilized as data sources to locate references related to cognitive interventions in individuals with MCI. The cognitive intervention study was required to have a control or alternative treatment comparison group to be included. Thirty articles met criteria, including six computerized cognitive interventions, 14 therapist-based interventions, and 10 multimodal (i.e., cognitive intervention plus an additional intervention) studies. Small, but significant overall median effects were seen for ADLs ($d = 0.23$), mood ($d = 0.16$), and metacognitive outcomes ($d = 0.30$), but not for QOL ($d = 0.10$). Computerized studies appeared to benefit mood (depression, anxiety, and apathy) compared to controls, while therapist-based interventions and multimodal interventions had more impact on ADLs and metacognitive outcomes than control conditions. The results are encouraging that cognitive interventions in MCI may impact everyday life, but considerably more research is needed. The current review and meta-analysis is limited by our use of only PsychInfo and MEDLINE databases, our inability to read full text non-English articles, and our reliance on only published data to complete effect sizes.

Keywords

Mild Cognitive Impairment; Cognitive intervention; Activities of daily living; Quality of life; systematic review; meta-analysis

Introduction

Research into interventions for Mild Cognitive Impairment (MCI) has been growing exponentially since the turn of the twenty-first century. The concept of MCI was formulated almost 20 years ago now (Petersen et al. 1999; Smith et al. 1996) to help focus research and

clinical practice on people at risk for but having not yet developed dementia. MCI is characterized by 1) a cognitive concern, 2) cognitive impairment on psychometric testing, 3) largely intact activities of daily living (ADLs), and 4) not meeting criteria for dementia (Albert et al. 2011). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition utilizes this concept of MCI in their diagnostic designation of Minor Neurocognitive Disorder (American Psychiatric Association 2013). Frequently, the cognitive problems experienced by individuals with MCI negatively impact their lives, including mood, relationships, treatment compliance, and independence.

MCI was once viewed as a condition that was not conducive for rehabilitation because of its likely progressive course to dementia. However, there has been increasing interest in whether individuals with MCI can benefit from cognitive intervention and rehabilitation techniques. A cognitive intervention is an intervention aimed to positively impact the cognitive functioning of an individual. To further operationalize types of cognitive interventions, Linda Clare and her colleagues (2003) advocate distinguishing the concepts of cognitive stimulation, cognitive training, and cognitive rehabilitation. Cognitive stimulation usually refers to activities that are not aimed towards a systematic improvement of a particular cognitive domain, but rather cognitive activity that is thought to be “stimulating” and good for the brain in general. Cognitive training usually involves manualized training to aid function in a particular cognitive domain, such as memory, language, or problem solving. Cognitive rehabilitation usually refers to a more individualized approach based on goal setting with the person and often their family member(s). Several early reviews into cognitive interventions in MCI were published between 2008 and 2012, including a Cochrane Review of published randomized controlled trials (RCT) through 2007 that found little evidence for the benefit of cognitive interventions in MCI (Martin et al. 2011). Less strict reviews (i.e., those not requiring RCTs at that early stage of the field) were more positive, noting hopeful outcomes on cognition, mood, and daily life after cognitive rehabilitation (e.g., Tsolaki et al. 2011; Gates et al. 2011).

Repeatedly, these reviews pointed to a need for larger trials, randomized control groups, and consistency in outcomes measured (Belleville 2008; Jean et al. 2010a; Stott and Spector 2011; Hampstead et al. 2014). The few reviews that set out to perform meta-analyses were stymied by the wide variety of methods employed in the cognitive interventions and variable outcomes measured (e.g., Gates et al. 2011; Kurz et al. 2011; Cooper et al. 2013). Li et al. (2011) did perform a meta-analysis on studies containing either a cognitive or functional outcome but not all of the studies were controlled trials (CTs). They found a moderate impact on language ($d = 0.51$), episodic memory (0.45), anxiety (0.51), and functional ability (0.55), but little effect on other areas of cognition, quality of life (QOL), or depression. They noted, as have others (Martin et al. 2011), that the effect sizes were smaller in the controlled studies compared to the single arm studies.

Few reviews have looked at the everyday impact of cognitive interventions in MCI, and some have even required a cognitive outcome measure for inclusion in the review (e.g., Reijnders et al. 2013). Lack of focus on real-world impact outcomes appears to be particularly true in computer-based interventions (Lampit et al. 2014). While requiring a cognitive outcome in a cognitive intervention trial may at first seem straight forward, the

underlying assumption is that cognitive interventions in MCI are meant to ameliorate decline or even restore cognitive ability. However, the goals of cognitive interventions or cognitive rehabilitation are not exclusively meant to restore cognition. In rehabilitation, the focus can be on impacting the ability itself by returning it to its baseline (restorative) or at least improving it to some degree (remediation), or the focus can be on helping an individual adapt to the changed ability without attempting to improve the ability itself (compensation). Both can be addressed in rehabilitation simultaneously as well.

In the case of MCI due to a neurodegenerative condition, the pathological burden in the brain by time of symptom onset is often substantial. Restoring innate memory or other cognitive ability at this point may not be feasible. Rather, the goal may often be compensation or adaptation to a lost ability, where no improvement in measured cognitive ability is expected. Thus, while some reviews may find moderate to large effect sizes for memory outcomes (e.g., Gates et al. 2011), it is not surprising that some reviews find little impact on standardized neuropsychological tests (e.g., Simon et al. 2012; Cooper et al. 2013).

Most recently, when performing a systematic review of all types of nonpharmacological intervention in MCI (i.e., a mix of cognitive therapy interventions, physical exercise programs, and psychotherapy interventions), Rodakowski and colleagues (2015) noted the continued infrequency of source articles and reviews focused on everyday life impact and not just cognitive outcome. Only 50 % of the studies in their review conducted through November 2014 actually measured such impact. They found that remediation based interventions appeared to have the largest impact on cognitive variables, and compensation based interventions showed promise to have a larger impact on everyday functioning variables. Despite this, most articles appear to continue to relegate these daily impact measures to “secondary outcomes” or “other treatment targets” behind the primary cognitive outcomes. This is unfortunate, as individuals with MCI and their partners have been shown to report quality of life and self-efficacy as the most important outcomes they want to see addressed in cognitive intervention programs (Barrios et al. 2016).

Giebel and Challis (2015) searched the literature in May of 2013 and found only three cognitive intervention studies in MCI that had an everyday functional ability outcome. These authors noted that while these three studies were encouraging that cognitive training could improve ADLs in MCI, the studies lacked clear descriptions of the interventions, apparent non-standardized administration of the interventions, and weak theoretical rationale for choice of cognitive strategy. This undermined the interpretability of the impact of cognitive training on ADLs in MCI. Coyle et al. (2015) focused their systematic review on computerized interventions through January 2014 and found that eight of sixteen studies looked at mood and ADLs as secondary outcomes, and five of sixteen looked at metacognitive outcomes. Mood improvements were noted in a little under half of the computerized interventions that assessed mood, but none of the eight studies that looked at ADLs found change after the computerized intervention. This may be expected, as computerized interventions are usually remediation based rather than compensation based, and thus cognitive outcomes were more likely to show improvement.

The growth of cognitive intervention studies in MCI from the first published RCT in 2002 (Rapp et al.) to the date of this review is shown in Fig. 1. Given the significant growth of research in this area, and the dearth of reviews targeting daily life outcomes after cognitive intervention in MCI, we sought to determine if there had been a recent increase in the utilization of everyday outcomes in cognitive intervention trials in MCI. We focused our search on studies that compared everyday or “generalizability” outcomes in individuals with MCI who had received a cognitive intervention contrasted to a comparison group. We defined generalizability outcomes not as measured change in cognition, but rather the impacts on daily life to which the cognitive interventions may generalize or transfer. Specifically, this includes outcomes such as measures of ADLs, mood, QOL, or metacognitive outcomes (how one feels/thinks about one’s cognitive process). We organized these studies based upon what type of intervention was administered. Namely, studies were presented in groups of computerized interventions (where the goal is most often cognitive restitution), therapist-based interventions (where the goal is most often cognitive adaptation), and the emerging trend of multimodal interventions, where cognitive therapy is combined with other nonpharmacological interventions, such as physical exercise and/or psychotherapy (often with both cognitive restitution and adaptation goals).

Methods

Search Strategy

PRISMA guidelines were followed (Moher et al. 2009); however, the protocol was not registered. Using the Ovid interface, an experienced librarian searched the MEDLINE and PsychInfo databases based on the PICOS statement provided by the authors. Both searches were completed on October 30, 2015 and included all possible publications up until that date. There were no restrictions on language or publication date; however, the searches were limited to adult participants. Search strategy included MeSH and PsychInfo controlled vocabulary terms and keywords, including Mild Cognitive Impairment, MCI, cognitive therapy, and rehabilitation. The complete strategy can be found in the Appendix.

Inclusion and Exclusion of Publications

Two authors (MJC and GES) independently reviewed the list of potential articles produced by the search strategy. Criteria for including or excluding articles were determined a priori. Study participants had to be diagnosed with MCI (Petersen et al. 1999; Albert et al. 2011; Winblad et al. 2004). Cognitive interventions could include cognitive stimulation, cognitive training, or cognitive rehabilitation approaches (Clare et al. 2003). Articles were excluded in the following order of priority: 1) participants were not MCI, 2) there was no cognitive intervention, 3) the publication was a review rather than primary study, 4) the publication was not peer reviewed, 5) the sample included MCI, but was mixed with healthy elderly and/or dementia subjects and independent analysis of the MCI group was not provided, 6) the study was not a CT (either CTs or RCTs were acceptable), 7) there was no generalization outcome (e.g., only objective cognitive testing outcome), 8) the sample was a duplicate of another published paper without novel information (additional studies from the same sample were included if they represented an additional follow up point or different outcome variables), and 9) the status could not be determined because the article was not in English

(all had English abstracts and some could be excluded prior to this ninth criteria based upon that abstract).

Titles were first reviewed for obvious exclusions. If it was unclear whether the article should be excluded after reading the abstract, the full text was reviewed. Authors MJC and GES then compared their reviews of articles to ensure that the same studies had been excluded or included in the order of priority listed above. No metric of inter-rater reliability was assessed. Any discrepancies between the two authors were discussed, the full text articles consulted as needed, and an agreement reached on how to best classify the article. The application of these criteria assured that all studies included in this analysis were clinical trials involving generalization outcomes from cognitive or multimodal interventions delivered to exclusively MCI cohorts compared to a control/comparison group that were presented in a peer reviewed English language publication.

Extraction of Data from Articles

Articles to be included were divided into three subcategories: 1) computerized interventions, 2) therapist-based interventions, and 3) multimodal intervention articles, where a cognitive intervention (either computerized or not) was given as well as some other non-pharmacological intervention (e.g., physical exercise or psychotherapy). This method of grouping articles was conceptually based, and for organizational purposes. Three authors (MJC, GES, and ACP) independently extracted data from reading the full text articles to complete a priori created data tables. Tables with extracted data and articles were then reviewed by a second person for accuracy to ensure no errors. The data selected for extraction can be found in the columns of Tables 1, 2, 3, 4, 5, and 6.

Meta-Analysis

Meta-analysis was conducted (by MM and LJR) on all studies that included a comparison group that allowed us to isolate the unique effect of a particular treatment (e.g., no contact control, social contact control, or alternative treatment). Meta-analysis was restricted to available data in published manuscripts. Data was extracted from the articles (LJR) to calculate effect sizes for further use in the meta-analysis (MM). The variables utilized to calculate effect sizes are presented in Tables 2, 4, and 6. To provide a conservative test of effect, we used the most distal follow-up occasion available for each study; thus, if a study had an immediate posttest and 6- and 12-month follow-ups, only the 12-month follow-up was considered. For most studies, we quantified effect size as standardized mean difference (Cohen's *d*), using the formula:

$$\frac{[(\text{posttest mean}_{\text{treatment}} - \text{pretest mean}_{\text{treatment}}) - (\text{posttest mean}_{\text{control}} - \text{pretest mean}_{\text{control}})]}{(\text{pooled baseline standard deviation})}$$

This approach quantified the metric of change in terms of the original variability of the sample (so that a *d* = 1 would mean that the treatment group experienced one standard deviation more improvement than control). For all studies, standardized mean differences were coded so that positive values meant that the treatment group experienced more improvement (i.e., in the desirable direction) than the controls.

Following the recommendations of Field and Gillett (2010) we used random effects models to assess the magnitude of effects; generally speaking, random effects permit the generalization of findings beyond the specific sample of articles included in this study. Heterogeneity was quantified both in terms of the Q statistic, and tau squared (Hedges and Olkin 1985; Higgins and Thompson 2002; Higgins et al. 2003). To evaluate the effect of categorical moderator variables (i.e., therapy modality and outcome type) on effect sizes, we conducted a multiple regression via mixed model. The model assumed a general linear model in which each effect size could be predicted from the moderator, which was coded via dummy coded contrast weights, and which was estimated via generalized least squares (Field 2003; Overton 1998).

We also attempted quantitative estimates of the extent to which effect size estimates might show evidence of publication bias. Several methods were used to assess the magnitude of estimated publication bias and its impact on meta-analysis findings. First, for each group of studies, we estimated Rosenthal's (1979) Fail Safe N, which estimates the number of unpublished studies that would need to exist to turn a significant population effect size estimate into a non-significant one. Second, we employed the Begg and Mazumdar's (1994) rank correlation test for publication bias, which estimates Kendall's tau between a standardized form of the effect size and its associated variance; when the relationship is strong/significant, this signifies publication bias (Field and Gillett 2010). However, since the test lacks power for small meta-analyses, non-significant associations cannot be taken as evidence for the absence of bias. Third, we employed a sensitivity analysis approach described by Vevea and Woods (2005), which produces adjusted effect size estimates. This approach specifies four typical weight functions to adjust effect sizes, which they label "moderate one-tailed selection," "severe one-tailed selection," "moderate two-tailed selection," and "severe two-tailed selection."

Results

The initial search terms resulted in 463 articles for further review. Following the article inclusion/exclusion process (Fig. 2), 30 articles remained for inclusion. Of these, six were computerized interventions, 14 were therapist-based interventions, and 10 multimodal studies. In the multimodal studies, cognitive outcomes compared to a control group could be extracted from one additional computerized (Fiatarone Singh et al. 2014) and two additional therapist-based interventions (Lam et al. 2015; Nakatsuka et al. 2015). Thus, aspects of these studies appear in both analyses: the isolated cognitive intervention outcomes in the respective computerized or therapist-based intervention sections, and the cognitive intervention outcomes when combined with other nonpharmacological interventions in the multi-modal section.

Computerized Interventions Overview

We included six studies that involved computerized cognitive interventions and one additional multimodal study in which results from a computerized intervention could be extracted (seven total studies; see Tables 1 and 2). Only one (Talassi et al. 2007) of these seven studies was not a RCT. In this study, method of group assignment was not specified,

but it is unlikely that randomization was used given the notably unbalanced group sizes. Sample sizes ranged from 8 to 51 ($M = 21.3$, $SD = 15.2$) and 7 to 49 ($M = 17.7$, $SD = 14.7$) for the intervention group (IG) and the control groups (CG) respectively, based upon numbers at final follow-up. One study (Fiatarone Singh et al. 2014) was a clear outlier with the 51 and 49 participants in the IG and CG groups. Excluding that study, the mean across studies for IG was 16.3 ($SD = 8.5$) and CG was 12.5 ($SD = 5.6$).

Recruitment rates were not routinely reported. For those studies utilizing some approximation of CONSORT reporting guidelines (Schulz et al. 2010) recruitment rates ranges from 4.5 % (Fiatarone Singh et al. 2014; Hughes et al. 2014) for community samples to 33 % (Gagnon and Belleville 2012) for a clinical sample ($M = 37.8$; $SD = 36.8$). Pooled (intervention and control) retention rates ranged from 64 % (Maurice Finn and McDonald 2011) to 100 % (Hughes et al.; $M = 86.3$; $SD = 35.1$).

Sessions lasted from two weeks (Gagnon and Belleville 2012) to nine months (Rozzini et al. 2007), with a median of 25.5 h of intervention (range: 6–130). For four of seven studies, the last follow-up was end-of-treatment. Three studies (Fiatarone Singh et al. 2014; Gaitan et al. 2013; Hughes et al. 2014) ended treatment after 12 to 26 weeks but conducted delayed follow-ups at 12 to 18 months. The longest follow-up period reported was 18 months (Fiatarone Singh et al. 2014).

Group intervention was used in three studies while individual interventions were provided in four studies. Training programs targeting multiple cognitive domains were used in five of seven studies. Focused attention training was used in Gagnon and Belleville's (2012) study. Hughes et al. (2014) used a computer gaming intervention (Wii video games) that required not only attention but also movement.

Therapist-Based Interventions Overview

Of the 14 articles included, two represented the separate publications of treatment-end outcome (Buschert et al. 2011) and then longer-term follow up in the same sample (Buschert et al. 2012). Cognitive intervention only outcomes could be determined in one multi-modal, non-computer intervention (Lam et al. 2015). Thus, there are 14 studies presented in Tables 3 and 4. Of these, all were RCTs with the exception of one which was a CT (Belleville et al. 2006). Sample sizes ranged from seven to 145 for the intervention group ($M = 27.5$, $SD = 35.3$) and 4 to 131 ($M = 26.9$, $SD = 33.2$) for the control groups (based upon numbers at last follow-up). One study (Lam et al. 2015) was a clear outlier with 145 and 131 participants in the IG and CG groups. Excluding that study, the mean across studies for IG was 19.1 ($SD = 7.2$) and CG was 18.9 ($SD = 9.1$). Recruitment rates ranged from 36.0 to 91.3 % ($M = 68.4$, $SD = 19.6$). Attrition rates averaged 17.7 % ($SD = 7.4$), for a total retained sample size ranging from 65.2 to 90.9 %.

Sessions lasted from three weeks (Jean et al. 2010b) to 12 months (Lam et al. 2015). Hours of contact could be calculated in 12 of the 14 studies (excludes Finn and McDonald 2015; Rojas et al. 2013), ranging from 4.5 (Jean et al. 2010b) to 156 h (Lam et al. 2015). Excluding Lam et al. as an outlier, studies averaged 15.5 h of intervention ($SD = 10.1$). Participants were followed through training end in six of the 14 studies, and often the

waitlist control group was then allowed to participate in the intervention (Belleville et al. 2006; Brum et al. 2009; Kinsella et al. 2009; Konsztowicz et al. 2013; Troyer et al. 2008). The longest follow-up period reported was 28 months (Buschert et al. 2012).

The majority of the therapist-based intervention studies (11/14) utilized a group setting for their intervention, only three studies (Finn and McDonald 2015; Greenaway et al. 2013; Jean et al. 2010b) had solely individual sessions. Nakatsuka et al. (2015) had both group and in-home individual sessions. In terms of the therapy content, two studies focused exclusively on one specific type of learning strategy: repetition lag training (Finn and McDonald 2015) or errorless learning (Jean et al. 2010b). One study focused exclusively on training of an external memory (calendar) aid (Greenaway et al. 2013). Konsztowicz et al. (2013) contrasted a mnemonic memory training group, external aid calendar group, and a waitlist control. All the remaining studies (10/14) had a multicomponent “memory training” group that typically consisted of education about memory and memory loss, cognitive exercises, mnemonic training, as well as encouragement to use external aids without detailed training.

Multimodal Interventions Overview

Ten studies involving multimodal interventions were reviewed involving multimodal interventions (i.e., cognitive intervention plus another non-pharmacological intervention) with MCI patients and caregivers. Two of the studies had overlapping samples, but looked at MCI participant (Joosten-Weyn Banningh et al. 2011) and caregiver outcomes (Joosten-Weyn Banningh et al. 2013) separately and so both reports are included in separate table rows (see Table 5).

Of the 10 multimodal intervention studies reviewed, seven were RCTs and three were CTs. The study by Reuter et al. (2012) did not include a CG, and instead analyzed subjects randomly assigned to incremental levels of intervention ($N = 223$). MCI patient multi-modal IG sizes ranged from 6 to 132 ($M = 56.5$, $SD = 39.0$); one study analyzed caregivers in an IG with sample size of 58 (Joosten-Weyn Banningh et al. 2013). Two studies analyzed intervention groups with sample sizes of 100 or greater (Reuter et al. 2012; Tsolaki et al. 2011; Lam et al. 2015). Control group sizes ranged from 5 to 131 ($M = 43.8$, $SD = 40.8$) and an additional caregiver control group included of 27 participants.

Recruitment rates were examined in 7 of 10 studies (excludes Kurz et al. 2009; Hwang et al. 2012; Reuter et al. 2012). Rates ranged from 4.8 % (Fiatarone Singh et al. 2014) to 89.8 % (Tsolaki et al. 2011) of approached participants ($M = 54.4$ %; $SD = 31.2$). The former study was a clear outlier; in that study a large participant pool ($N = 2094$) was approached and only 100 eligible enrolled (4.8 %). Excluding this study, the average enrollment rate is 64.3 % ($SD = 21.9$ %). Two studies (Kurz et al. 2009; Tsolaki et al. 2011) did not publish data on participants lost to attrition. The average participant retention rate was 85.7 % ($SD = 9.0$ %).

The average duration of intervention was 16.6 weeks ($SD = 14.2$) and ranged from 4 weeks (Kurz et al. 2009; Reuter et al. 2012) to 52 weeks (Lam et al. 2015). An average of 52.2 h of intervention ($SD = 49.0$) was delivered across the 10 studies. Five studies (Fiatarone Singh et al. 2014; Hwang et al. 2012; Joosten-Weyn Banningh et al. 2011; Law et al. 2014; Reuter

et al. 2012) provided data from post-intervention follow-up assessments with intervals ranging from two to 52 weeks ($M = 23.0$, $SD = 15.6$), and Hwang et al. (2012) also followed-up with participants at three months post intervention.

Four studies combined cognitive training with physical exercise (Fiatarone Singh et al. 2014; Kurz et al. 2009; Lam et al. 2015; Reuter et al. 2012). Three studies used interventions with a combination of cognitive strategy training, psychoeducation, and social skills training components (Joosten-Weyn Banningh et al. 2011; Joosten-Weyn Banningh et al. 2013; Schmitter-Edgecombe and Dyck 2014). Two studies (Hwang et al. 2012; Law et al. 2014) utilized interventions with computerized and non-computerized cognitive training components. One study (Tsolaki et al. 2011) provided varying methods of non-computerized cognitive training (e.g., paper-and-pencil tasks, prospective memory training, etc.). Reuter et al. (2012) assigned groups to one of the following interventions: one group received cognitive training, relaxation, and occupational therapy; one group with the previously stated components plus a training skills application session; and one group with cognitive training, application session, and additional motor skills training.

Meta-Analysis

Overall Effects—A subset of six of the 30 articles reviewed could not be used, in whole or in part, in our meta-analysis due to failure to include sufficient information to compute standardized mean differences; of these, four papers contributed no information to the meta-analysis (Belleville et al. 2006; Fiatarone Singh et al. 2014; Finn and McDonald 2011; Reuter et al. 2012), and two contributed only one or two outcomes because of a lack of information about other outcomes in their paper (Hwang et al. 2012; Rojas et al. 2013).

Sample sizes included in the meta-analysis were smaller than the original, randomized sample sizes described above due to attrition by the most distal follow-up occasion utilized in the meta-analysis. Tables 2, 4, and 6 show the effect sizes for the studies included in the meta-analysis along with the residual treated and control sample sizes employed in the meta-analysis.

The mean effect size (d) representing the omnibus difference between improvement in the treatment versus control group was 0.21 in the fixed effects model (95 % confidence interval = 0.16–0.27, $SE = 0.03$), which was significantly different from zero ($z = 7.50$, $p < .001$, based on 91 outcome measures), with the Q-statistic indicating significant heterogeneity in effect size ($\chi^2 [90] = 185.88$, $p < .001$). In the random effects model, the mean effect size representing the difference between improvement in the treatment versus control group was 0.26 (95 % confidence interval = 0.17–0.35, $SE = 0.05$), which was significantly different from zero ($z = 5.71$, $p < .001$, based on the same 91 outcome measures). The Q-statistic, in contrast, indicated homogeneity in effect size ($\chi^2 [90] = 78.54$, $p = .80$). The tau estimate of variance in population effect size was 0.08. Rejection of the null hypothesis of homogeneity, at least in the fixed effect model, suggests that moderator models are indicated.

Variation in Effect Sizes by Treatment Modality and Outcome Type—Two tests for subgroup differences were conducted. The first examined differences between therapy type (i.e., computer administered, therapist administered, and multi-modal). The fixed effect

model indicated that this difference was significant ($\chi^2 [2] = 8.56, p = .01$). Table 7 displays the number of outcomes (k), mean standardized effect size (d), 95 % confidence interval, tau-squared (τ^2), and p-value for the Q-test assessing the null hypothesis of homogeneity within each therapy type as well as for each outcome category type. In all instances, the random effects models could not reject the null hypothesis of homogeneity, meaning that results were consistent within studies using similar intervention approaches. For all three intervention types, treatment effects were positive (average d statistics ranged between 0.20 and 0.31, corresponding to a “small” effect size) and significantly different from zero.

The second comparison of subgroup differences examined differences between outcome type (i.e., mood, meta-cognition, ADL, and QOL). The fixed effect model indicated that this difference was also significant ($\chi^2 [3] = 14.75, p = .002$). Reviewing the results in Table 7, for each of the four outcome types, the random effects models could not reject the null hypothesis of homogeneity, meaning that results were consistent within a group of outcomes. For mood, metacognition and ADLs, treatment effects were positive (average d statistics ranged between 0.16 and 0.37, corresponding to a “small” or “small to medium” effect size) and significantly different from zero. For QOL, average effect size was not different from zero.

We examined stem-and-leaf plots broken down by the intervention approach, and by outcome type. While the average standardized mean differences in most intervention modalities and outcome categories show clear evidence of symmetrical cluster, the averages may be biased upwards by positive skew. Thus, we also determined the, median effect sizes by therapy type were: median_{computer} = 0.17; median_{therapist} = 0.23; median_{multimodal} = 0.23. Median effect sizes by outcome category were: median_{mood} = 0.16; median_{metacognition} = 0.30; median_{ADL} = 0.23; median_{QOL} = 0.10. Once at the level of examining outcome category by intervention approach (e.g., mood outcomes by computerized intervention), the small number of variables per cell made reporting of aggregate effect size scores unreliable. Thus, qualitative analysis of these variables was further explored (below).

Computerized Interventions Outcomes

ADLs: Four of the seven studies included an assessment of basic and or instrument ADLs. No study reported a significant benefit to ADLs from cognitive training.

Mood: Four studies included a mood measure. Two of three studies employing the Geriatric Depression Scale (GDS; Yesavage et al. 1983) reported improved scores on this instrument. Two studies employing the State Trait Anxiety Inventory, State Scale (Spielberger 1983) reported improved scores on this instrument. In one of those studies end of treatment findings were negative but 12 month follow-up findings were positive. In a study also employing the Neuropsychiatric Inventory (Cummings et al. 1994) an informant-based measure of observed mood and behavior, NPI total was improved due to lower scores of perceived depression, anxiety, and apathy. Finally, one additional study using an integrated depression, anxiety, and stress scale (Depression, Anxiety and Stress Scale, DASS-21; Lovibond and Lovibond 1995) found no impact of computer training in any of these three domains.

QOL: Only one study (Gagnon and Belleville 2012) included a well-being scale. They found no impact of training on this scale.

Metacognitive: In four different studies, participants used five different instruments to report on their perceptions of cognitive function. In three of those four studies, computer training did not have an impact on reported cognitive function. In these studies, the cognitive self-report measures all focused on perception of memory function. Only in Gagnon and Belleville (2012), where both training and the self-report measure focused on attention, was there a positive finding.

Summary: Computerized cognitive training in MCI did not appear to impact ADL measures or measures of self-reported memory function. Evidence for an impact on mood was mixed, with some studies reporting improvement in depression, anxiety, and perhaps apathy. There was not enough research to comment on the impact of computerized training on QOL.

Therapist-Based Interventions Outcomes

ADLs: ADLs were assessed in 10 therapist-based intervention studies, and of those studies, half found some positive benefit to daily activities (Brum et al. 2009; Greenaway et al. 2013; Konsztowicz et al. 2013; Rojas et al. 2013; Rapp et al. 2002). There was little overlap in the measures that were used to determine ADLs, but four studies used the Multifactorial Metamemory Questionnaire (MMQ; Troyer and Rich 2002) Ability Subscale with only one finding significant benefit from memory training on that measure (Konsztowicz et al. 2013).

Mood: Mood was assessed in 12 studies, with only three studies reporting significant change (Buschert et al. 2011; Konsztowicz et al. 2013; Lam et al. 2015). Kinsella et al. (2009) actually found improved mood over time in their control group contrary to their hypothesis. Buschert et al.'s report of mood improvement at training end was diminished by 15-month follow up (2012). There was little consistency in measures used, but four used the MMQ Contentment Subscale. Similar to the ADL findings, only Konsztowicz et al. (2013) reported improved contentment in their memory-training group.

QOL: QOL of assessed in six studies, with only two reporting significant improvement after intervention (Vidovich et al. 2015; Belleville et al. 2006). The most commonly used measure was the Quality of Life AD (Logsdon et al. 2002), used in three studies, only one of which was significant (Vidovich et al. 2015).

Metacognitive: Participants' sense of their memory or memory strategy use was assessed in 10 studies. Six studies had positive results (Belleville et al. 2006; Kinsella et al. 2009; Lam et al. 2015; Rapp et al. 2002; Troyer et al. 2008; Vidovich et al. 2015). The MMQ Strategy Use (self-reported memory strategy use) was the most often cited measure (4 out of the 10 studies).

Other: Greenaway et al. (2013) reported the impact of the intervention on caregivers, with no effect on caregiver QOL or anxiety, but less sense of caregiver burden and depression compared to the control group by six months post intervention. Buschert et al. (2012) reported that 6 out of 12 of their CG had converted to dementia by eight months post, while

none of their IG had converted. Vidovich et al. (2015) found that 6.7 % of their CG and 11.9 % of their IG had converted to dementia at two years, but 45 % of their CG and 37 % of their IG group had reverted to normal by two year follow-up.

Summary: The strongest evidence for everyday impact of therapist-based interventions was for the improvement of metacognitive aspects of memory. After these cognitive interventions, individuals with MCI believed they knew more strategies to help with their memory and/or had more sense of self-efficacy surrounding their memory function. Additionally, about half of studies demonstrated positive impact on ADLs, particularly when practical compensation strategies were taught. This translated into little evidence for improving mood or QOL in the participant with MCI, but there may be some positive caregiver outcomes.

Multimodal Interventions Outcomes

ADLs: Six of the 10 multimodal intervention studies assessed ADL outcomes, of which four reported significant improvements. Two studies saw improvement on ADL rating scales with cognitive plus physical interventions (Kurz et al. 2009; Lam et al. 2015) and one saw positive impact with cognitive plus psychological interventions (Tsolaki et al. 2011). Schmitter-Edgecombe and Dyck (2014), using cognitive plus psychological interventions, found improvements on performance-based measures of ADLs involving bill-paying and money management activities. Two studies utilizing the Bayer-ADL scale (B-ADL; Hindmarch et al. 1998) saw inconsistent improvement. One study using both computerized and non-computerized cognitive training (Law et al. 2014) provided follow-up analyses that showed no sustained improvement in ADLs at 6-months follow-up.

Mood: Mood outcomes were mixed (assessed in 4/10 studies), with two cognitive plus physical interventions (Kurz et al. 2009; Lam et al. 2015) showing improvement, and two cognitive plus psychological interventions (Joosten-Weyn Banningh et al. 2011; Schmitter-Edgecombe and Dyck 2014), showing no improvement upon intervention end. The two studies that did not find improvements in mood used a short form version of the GDS (Yesavage et al. 1983). No study assessed mood at a post-intervention follow-up.

QOL: QOL was assessed in four of the studies (Hwang et al. 2012; Joosten-Weyn Banningh et al. 2011; Reuter et al. 2012; Schmitter-Edgecombe and Dyck 2014), and most of these studies identified no impact. QOL improved in a cognitive plus psychological training intervention (Joosten-Weyn Banningh et al. 2011) using the RAND-36-Dutch (Van der Zee and Sanderman 1993). In this study, the Helplessness subscale of the Illness Cognition Questionnaire (ICQ; Evers et al. 2001) was sensitive to change following the intervention; however, the ICQ Acceptance subscale did not show improvement. The intervention group from Reuter et al. (2012) received the most intensive treatment (i.e., cognitive and motor training with practice) saw QOL improvements. No lasting impact on QOL was seen at 2-week or 3-month follow-up intervals.

Metacognition: Metacognitive outcomes were assessed in four of the 10 studies with generally improved outcomes. Hwang et al. (2012) showed improvement using a

computerized plus non-computerized cognitive intervention on a self-assessment of cognition scale at 2-week follow-up; however, these improvements were not sustained at three months. Multi-modal interventions showed positive impact on self-reported and informant based cognitive complaints (Lam et al. 2015; Joosten-Weyn Banningh et al. 2011) but not in self-reported coping self-efficacy (Schmitter-Edgecombe and Dyck 2014).

Other: Two studies using cognitive plus psychological interventions analyzed the impact on mood, QOL, and metacognition in caregivers (Schmitter-Edgecombe and Dyck 2014; Joosten-Weyn Banningh et al. 2013). No improvements were found for mood, but one scale of well-being indicated an improvement in QOL of caregivers (Joosten-Weyn Banningh et al. 2013). Positive findings were found on scales of coping self-efficacy (Schmitter-Edgecomb and Dyck 2014) and awareness of the MCI participant's cognitive symptoms (Joosten-Weyn Bannigh et al. 2013).

Summary: Although more studies found no impact on ADLs than benefit; the improvements in ADLs were seen mostly in the cognitive plus physical interventions studies. Mood improvements, particularly for depression, were mixed overall. But again, the studies that found improvements in mood were cognitive plus physical interventions. There was little evidence for impact of multimodal interventions on QOL. Metacognitive outcomes were generally positive across multi-modal interventions. Preliminary evidence suggests potential positive benefit in caregiver outcomes when cognitive plus psychotherapy interventions are used. Overall, the most favorable outcomes tended to be in multimodal studies that combined interventions with cognitive and physical training.

Publication Bias—For the overall corpus of studies, Rosenthal's Fail Safe N was 2295, indicating that there would need to be 2.295 unpublished studies not included in the meta-analysis to make the population effect size non-significant. Begg and Mazumdar's rank correlation (tau) was .17 ($p = .02$) indicating small but non-trivial publication bias. Random-effects weighted effect size estimates under the conditions of 'moderate one-tailed selection', 'severe one-tailed selection', 'moderate two-tailed selection', and 'severe two-tailed selection' were 0.15, -0.84, 0.21 and 0.16 respectively; this pattern of results suggests, congruent with our confidence interval and stem-and-leaf information noted earlier, that the overall average effect of 0.26 may be positively biased.

For the moderator analyses examining variation in effects by therapy modality and outcome type, we have included the publication bias statistics in Table 7. In general, these findings suggest that for the three different intervention types and four different outcome types, the results are affected by mild publication bias.

Discussion

Cognitive interventions in MCI have received increased interest from the international research community. Our review of the literature suggests that cognitive interventions in MCI have the potential for positive impact, but as previous authors have suggested (Cooper et al. 2013; Gates et al. 2011; Kurz et al. 2011), the heterogeneity of interventions and outcome measures used make it difficult to determine the everyday impact.

By looking at trends across studies, we can speculate what the potential impact might be. First, an overall meta-analysis combining all intervention and outcome types suggests that cognitive interventions in MCI cohorts have a small, positive effect on everyday outcomes. Therapist-based, computer-based, and multi-modal interventions all appear to have small but significant effects on everyday outcomes. These effects are seen in mood, ADL and meta-cognition measures but, at least for the studies included here, not in QOL outcomes. The effect size estimates reported here were likely conservative, as we used the most distal follow-up occasion available, which may have reduced the estimated effect sizes due to treatment effect dissipation over time.

Computerized interventions tend to be more restitution based, focus more on post-training cognitive outcomes, and are suspected to have limited far transfer to everyday measures (Coyle et al. 2015). However, in this review, participation in computerized cognitive interventions appeared to have the potential to positively impact mood. Some studies report improvement in depression, anxiety, and perhaps apathy. There was little evidence for improved mood from therapist-based cognitive training interventions.

When the intervention takes place with a therapist, either individually or in a group format, positive impact on ADLs is more often observed. Computer based interventions did not impact ADLs. The focus of therapist interventions is more often on compensation strategies (either internally-based mnemonic strategies or externally-based aids such as calendars). Perhaps this focus translates more readily to daily activity ability, as has been suggested previously (Rodakowski et al. 2015). Therapist-based interventions also have promise for improvement of metacognitive aspects of memory, such as how equipped a person feels with regard to strategies to combat memory loss, and/or use memory strategies (i.e., memory self-efficacy). There was little evidence of benefit to metacognitive variables from computerized training.

Recently, studies of multimodal interventions have emerged into the literature. These interventions seek to explore the benefits of cognitive interventions combined with other promising nonpharmacological interventions like exercise and socialization/psychotherapy. Many of these studies have employed therapist-based interventions, and the findings of impact on ADLs, mood, and metacognitive variables largely mirror the single-modality cognitive intervention literature. Combining physical and cognitive interventions appear to be particularly beneficial.

There was an absence of QOL effects across cognitive interventions. This likely reflects several factors. First, QOL is a complex construct with many inputs (e.g., health, economic status, and social factors), so cognitive interventions might have only partial effects. Secondly, interventions have investment costs; they are effortful, demanding of time, and may expose weaknesses that participants were not previously aware of prior to being challenged by training exercises. All of these could be expected to have negative impacts on reported QOL, particularly at the follow-up period immediately after treatment. It should be noted that these studies employed cognitive interventions. It may be that the inclusion of more direct “training for transfer” (i.e., including cognitive intervention

exercises that specifically address outcomes like ADL, mood, metacognition and QOL rather than targeting cognition itself) may have further strengthen treatment generalization.

In this updated review, we sought to explore whether prior admonitions for this area of research to employ larger trials, RCTs, and consistency in outcomes have been heeded. Newer studies, particularly multimodal intervention studies, have used larger samples, although the average number of individuals in each arm of trials still averages less than 30. Only a few studies report sample sizes in the hundreds. Our review is encouraging that more studies with larger samples are appearing. It is also encouraging that in these trials recruitment rates ($M = 58\%$) and retention rates ($M = 84\%$) are compatible with what is seen in other clinical trials such as pharmacological trials (Grill and Karlawish 2010) despite the often significant time commitment.

When we set our inclusion and exclusion a priori for this review, we did not limit to RCTs, but allowed CTs for inclusion. We actually found that a good number of recently conducted trials were RCTs. The field appears to be progressing beyond small, uncontrolled feasibility studies into larger RCTs. Because of this, future reviews can likely limit their analyses to RCTs

Consistency in interventions and outcome variables remain key issues to overcome in this literature. Most researchers appear to have created their own unique sets of cognitive interventions and outcome measures. Many past studies were likely happening at the same time, inspired by the few early works. Thus, unless they adopted outcome measures from these first few studies (e.g., using the MMQ as Kinsella et al. 2009, and Troyer et al. 2008, did in their early works), researchers were utilizing unique measures based on their own experiences and research. Moreover, the locations where this research was conducted (presented in Tables 1, 3, and 5) reflect just how international the research on cognitive interventions for MCI truly has become. The global nature of this effort likely also contributes to the variety of interventions and outcomes as multiple cultures and languages seek to address cognitive rehabilitation in MCI.

The commonly used measures in this area of research can be found in Tables 2, 4, and 6. For ADLs, we frequently saw the BADL (Hindmarch et al. 1998) used. The second most commonly used measure of ADLs was the Clinical Dementia Rating Scale (CDR). The GDS (Yesavage et al. 1983) was most often used in assessing mood, and more specifically, depressive symptom outcomes. QOL was assessed most commonly with the Quality of Life-Alzheimer's disease (Logsdon et al. 2002). Metacognitive outcomes were most often examined with the Memory Functioning Questionnaire (MMQ; Gilewski et al. 1990) or the Metamemory Questionnaire (MMQ; Troyer and Rich 2002). The MMQ is one of the most widely used instruments in general. This measure has subscales that examine ADLs (MMQ Ability) and mood/QOL (MMQ contentment), so researchers often present all of these aspects in their results. These instruments provide a good starting point to know what may be useful in finding effect (e.g., the MMQ metacognitive scales), and those that perhaps may be insensitive to finding change in the MCI population (e.g., the CDR may not sample enough higher level ADLs). Other reviews further point out methodological steps that could

add consistency to cognitive intervention research in MCI (Hampstead et al. 2014; Huckans et al. 2013).

Our systematic review and meta-analysis is limited by searching only MEDLINE and PsychInfo databases. Thus, some studies may have been missed. We also excluded four non-English studies due to our limited resources to translate them into English. Additionally, we were unable to solicit missing information from 6 studies to complete effect sizes and include them into the meta-analysis. Our findings may have been different had these additional studies/variables been added.

Further, we allowed for the inclusion of both CTs and RCTs in this review. We found that while most studies used a no-treatment control group, other studies, particularly the computer-based interventions, at times used suspected active control interventions, educational series, or even an alternative intervention suspected to not impact cognition in the same way as the experimental intervention. The differentiation between what truly was an active control and to what degree the education or alternative intervention would not impact cognition or the everyday functioning variable regularly was not well established in the articles, and was most often solely theoretically based. It is unclear if some impact of these suspected “active control” interventions may have tempered the effect sizes of these studies.

A key question in meta-analysis is the issue of publication bias. That is, to what extent might publication bias lead to an inflated or distorted estimate of true effect sizes? Concerns about publication bias likely hold for this corpus of thirty studies: (A) We did not solicit unpublished papers from outside the search databases listed; (B) We did not consult clinical trials registries to identify additional registered trials that have not been published; and (C) Published papers will be biased towards those with significant findings (Coursol and Wagner 1986; Greenwald 1975). However, it is noteworthy that most of the reviewed studies had a primary aim of having cognitive effects. Thus, most the outcomes considered in this review were in fact secondary, transfer outcomes for these studies. Often these everyday impact measures were given only a brief mention in the final paragraph of the results or embedded in a table without further explanation. This incidental reporting of positive or negative secondary results may have mitigated publication bias effects to some degree in this meta-analysis of everyday outcomes.

Indeed, our quantitative explorations of publication bias suggested the presence of relatively minor positive bias. For the overall set of studies, and for the subgroups of therapy modalities and outcomes, results suggested that anywhere from three to fifteen times the number of included studies would have to have been left out for significant d statistics to become non-significant. Rank correlation tested indicated generally only small associations between d and its standard error, suggestive of at most mild bias. Taken together, while publication bias undoubtedly influences the average effect sizes reported here, we have reason to believe that the median effect sizes and 95 % confidence intervals (all but one of which excludes $d = 0.00$) likely include the true population effect size.

Substantial research is still needed to determine the basic “active ingredients” of cognitive training and behavioral interventions in MCI, including the specific and non-specific treatment effects, dosing (i.e., number of sessions over what time frame), best training context (e.g., group vs. individual), participant variables affecting specific outcomes, etc. Further, research into how combining multiple nonpharmacological interventions may have synergistic impacts on everyday outcomes will perhaps produce the most effective “treatment sets” for MCI. Ideally, one day it will be possible to tailor treatment plans, using evidence-based interventions, to the outcomes that patients define as most important to them. Until then, much more investigation is needed to determine the impact of cognitive interventions on everyday outcomes in MCI, as, to date, only modest overall effect sizes were found in this meta-analysis.

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Appendix

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

1. mild cognitive impairment/ or (mci or amci or mci-a or predement* or pre-dement* or pre-AD or (mild adj2 cogniti* adj2 (decline or impair* or deficit* or deteriorate* or disorder*)) or ((prelude or preclinical or pre-clinical or prodromal or precursor) adj2 (dement* or Alzheimer* or AD))).tw
2. rh.fs or cognitive therapy/ or ((cogniti* or behavi* or memory or attention or information or neuropsychological or rehearsal* or mnemonic) adj3 (intervention* or rehab* or program* or strategy* or train* or retrain* or treatment* or therapy or therapies or stimulat* or technique*).tw
3. 1 AND 2
4. limit 3 to (addresses or autobiography or bibliography or biography or case reports or classical article or comment or dictionary or directory or editorial or historical article or in vitro or interactive tutorial or interview or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits or technical report)
5. 3 NOT 4
6. (infant* OR infancy OR newborn* OR baby* OR babies OR neonat* OR preterm* OR prematur* OR postmatur* OR child* OR schoolchild* OR school age* OR preschool* OR kid or kids OR toddler* OR adoles* OR teen* OR boy* OR girl* OR minors* OR pubert* OR pubescen* OR prepubescen* OR paediatric* OR paediatric* OR peadiatric* OR nursery school* OR kindergar* OR primary school* OR secondary school* OR elementary school* OR high school* OR highschool* or youth).tw
7. 5 NOT 6
8. 7 not (exp neoplasms/ or epilepsy/ or (schizophren* or cancer* or neoplas* or epilep*).tw.
9. (treatment outcome/ or treatment failure/ or quality of life/ or activities of daily living/ or mental recall/ or (outcome* or efficac* or effectiv* or benefit* or ((daily adj2 activit*) or (self* adj care*1))).tw. or ((pre* or post*) adj interven*).tw)
10. 8 AND 9

PsychInfo 1967 to October Week 3 2015

1. (mci or amci or mci-a or predement* or pre-dement* or pre-AD or (mild adj2 cogniti* adj2 (decline or impair* or deficit* or deteriorate* or disorder*)) or ((prelude or preclinical or pre-clinical or prodromal or precursor) adj2 (dement* or Alzheimer* or AD))).tw
2. exp. cognitive techniques/ or exp. neuropsychological rehabilitation/ or ((cogniti* or behavi* or memory or attention or information or neuropsychological or rehearsal* or mnemonic) adj3 (intervention* or rehab* or program* or strategy* or train* or retrain* or treatment* or therapy or therapies or stimulat* or technique*))).tw.
3. 1 AND 2
4. NOT (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur* or postmatur* or child* or schoolchild* or school age* or preschool* or kid or kids or toddler* or adoles* or teen* or boy* or girl* or minors* or pubert* or pubescen* or prepubescen* or paediatric* or paediatric* or peadiatric* or nursery school* or kindergar* or primary school* or secondary school* or elementary school* or high school* or highschool* or youth).tw.
5. limit 4 to (bibliography or "column/opinion" or "comment/reply" or editorial or encyclopedia entry or letter or obituary or poetry or publication information or reprint or review-book or review-media or review-software & other or reviews)
6. 4 NOT 5
7. AND (treatment outcomes/ or treatment effectiveness evaluation/ or exp. quality of life/ or exp. activities of daily living/ or exp. recall learning/ or (outcome* or efficac* or effectiv* or benefit* or ((daily adj2 activit*) or (self* adj care*1))).tw or ((pre* or post*) adj interven*).tw.)
8. not (exp neoplasms/ or epilepsy/ or (schizophren* or cancer* or neoplas* or epilep*))).tw.

Fig. 1.

Cumulative growth of controlled trials of cognitive interventions in MCI over time. To fully illustrate the total number of studies in this area, studies that included no generalization outcome measure (i.e., controlled trials of cognitive interventions in MCI that only provided cognitive measures or fMRI outcomes) that were excluded from the general review are shown in this figure as “Non-gen outcome”

Fig. 2. PRISMA Flow Diagram. Flow diagram illustrating the process of inclusion/exclusion of studies

Overview of Computerized Intervention Studies

Table 1

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Fiatarone Singh et al. (2014); Australia	RCT	MCI ^a (n = 24)	MCI ^a Sham cognitive activity and exercise control condition (n = 27)	Recruitment: 2094 Approached 2,094 research participants, 1994 Not eligible (1582 not interested, 217 on hold, 117 ineligible, 61 no contact, 17 withdrawals), 100 enrolled Attrition: 14 dropped out before intervention, 12 dropped out after intervention	COGNIPACK® computer program: adaptive exercises of memory, EF, attention, and processing speed, and sham physical training	2–3 sessions per week for 6 months or 52–78 sessions 60–100 minutes	6 months (intervention end) 18 months (12 months post intervention)	No significant improvement
Finn & McDonald (2011); Australia	RCT	aMCI ^b single and multiple domains (n = 8)	aMCI ^b single and multiple domains Waitlist (n = 8)	Recruitment: 27 people recruited from memory clinic 2 excluded prior to randomization, 12 randomized to intervention, (3 withdrawals in IG, 1 additional exclusion), 13 to control, (4 withdrawals 1 additional exclusion) Attrition: None	Lumosity program	30 sessions, for 6 weeks	Intervention end	Improved visual sustained attention, no treatment effect on visual learning, recognition, working memory or set shifting
Gagnon & Belleville (2012); Canada	RCT	MCI ^a (n = 12)	MCI ^a Active computer training (n = 12)	Recruitment: Approached 79 candidates from memory disorders clinics, 53 excluded, 26 randomized, 13 randomized to each group Attrition: 2 did not complete	Variable priority attention training	6 sessions 1 hour sessions spread of 2 weeks	Intervention end	Both groups improved on focused attention, speed of processing, and switching
Gaitan et al. (2013); Spain	RCT	aMCI ^a single and multiple domains (n = 23)	aMCI ^a single and multiple domains. Traditional cognitive training (n = 16)	Recruitment: 60 candidates randomly selected from pool of 93 interested, 37 randomized to intervention (6 refused or did no complete baseline), 23 to control (3 refused or did not complete baseline) Attrition: 11 withdrew prior to 3-month f/u; 1 outlier in each group excluded	Group-based FesKits computer program	30 sessions 30-minute computer sessions embedded in 1-hour traditional cognitive therapy session	3 months 12 months	No significant improvement
Hughes et al. (2014); USA	RCT	MCI (n = 10)	MCI Healthy aging education (n = 10)	Recruitment: Approached MYHAT participants, 445 eligible, 128 initially interested, 91 contacted 71 excluded (not interested, unable to contact, ineligible, not available)	Group-based Nintendo Wii™ video game	24 session, 90 minute weekly sessions for 24 weeks	Intervention end 1 year	CAMCI 24 weeks/+ 1 year/–

Reference/Location	Type	IG	CG	Recruitment/Atrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Rozzini et al. (2007); Italy	RCT	aMCI ^a (<i>n</i> = 15)	aMCI ^a AChEI only (<i>n</i> = 22) aMCI ^a No treatment (<i>n</i> = 22)	No information	TNP computer program	3 blocks of 20 1-hr sessions, 60 total sessions for 9 months	1 year	Improvements in story memory and abstract reasoning ^g
Talassi et al. (2007); Italy	CT	MCI ^a (<i>n</i> = 30)	MCI ^a Non-cognitive activities (physical therapy, occupational therapy, and behavioral therapy) (<i>n</i> = 7)	Recruited from a day rehabilitation hospital	TNP computer program, occupational therapy of ADLs, and behavioral therapy	12 sessions 4 days per week for 3 weeks	Intervention end	No significant improvement

Note. MCI criteria used:

^aPetersen et al., 1999 or 2004;

^bWinblad et al., 2004;

^cAlbert et al., 2011;

^dMorris, 1993;

^ePortet et al., 2006.

AChEI = Acetylcholinesterase inhibitor. aMCI = Mild cognitive impairment, amnesic subtype. CG = control group. CT = Controlled trial. f/u = Follow-up. IG = Intervention group. MCI = Mild cognitive impairment. RCT = Randomized controlled trial.

^gWithin-subjects change.

Interventions: COGNAPACK[®] (Marker 2008). FesKits (Fundacio Privada Espai Salut 2009). Nintendo Wii[™] (Nintendo of America Inc., Redmond, WA). TNP (Sinforiani et al. 2004).

Measures: C/MCI (Computerized Assessment of Mild Cognitive Impairment; Saxton et al. 2009)

Table 2

Everyday Outcomes for Computerized Intervention Studies

Reference	ADLs	Mood	QOL	Metacognition	Other
Fiatarone Singh et al. (2014)	Bayer-ADL/-				
Finn and McDonald (2011)		DASS-2 Subtests: Depression/- Anxiety/- Stress/-		MFQ/- MCI/-	
Gagnon and Belleville (2012)			WBS/- (<i>d</i> = 0.16, 12, 12)	DAQ/+ (<i>d</i> = -0.26, 12, 12)	
Gaitan et al. (2013)		GDS 3 month/- 12 month/- STAI-State 3 month/- 12 month/+ (<i>d</i> = 0.16, 23, 16)		MFEM 3 months/- 6 months/- (<i>d</i> = 0.56, 23, 16)	
Hughes et al. (2014)	Timed IADL/- (<i>d</i> = -0.12, 10, 10)				Walking speed: -
Rozzini et al. (2007)	BADL/- (<i>d</i> = 0.18, 15, 25)	GDS [§] /- (<i>d</i> = 0.17, 15, 15) NPI [§] /+ (<i>d</i> = 0.84, 15, 15)		CSRQ-25: - (<i>d</i> = 0.89, 10, 10)	
Talassi et al. (2007)	BADL/- (<i>d</i> = 0.0, 30, 7) IADL/- (<i>d</i> = 0.0, 30, 7)	GDS [§] /+ (<i>d</i> = 0.20, 30, 7) STAI [§] /+ (<i>d</i> = 0.09, 30, 7) NPI [§] /+ (<i>d</i> = 0.84, 30, 7)			Physical performance test/-

Note. Measures are provided with + or - to reflect whether the outcome was significant. When it was possible to calculate effect size, those numbers are provided next to the relevant test (effect size, final number of participants treated by that time point, final number of comparison participants by that time point). Positive effect sizes reflect greater improvement for treatment group relative to comparison group). Outcomes without an effect size did not provide information necessary to compute standardized mean differences.

[§]Within-subjects change.

Measures: BADL (Bayer-Activities of Daily Living; Hindmarch et al. 1998); CSRQ (Cognitive Self-report Questionnaire; Spina et al. 2006); DASS-21 (Depression Anxiety Stress Scale; Lovibond and Lovibond 1995); DAQ (Divided Attention Questionnaire; Tun and Wingfield 1995); GDS (Geriatric Depression Scale; Yesavage et al. 1983); IADL (Instrumental Activities of Daily Living; Lawton and Brody 1969); MCI (Memory Controllability Inventory; Lachman et al. 1995); MFEM (Memory Failures in Everyday Memory; Sunderland et al. 1984); MFQ (Memory Functioning Questionnaire; Gilewski et al. 1990); NPI (Neuropsychiatric Inventory; Cummings et al. 1994); STAI (State Trait Anxiety Inventory; Spielberger 1983); WBS (Well-Being Scale; Bravo et al. 1996).

Table 3

Overview of Therapist-based Intervention Studies

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Belleville et al. (2006); Canada	CT	aMCI ^a (single or multi domain) (<i>n</i> = 17)	aMCI ^a Waitlist (<i>n</i> = 8)	Recruitment: No information Attrition: 2 did not complete, 1 excluded from analysis from arthritis that interfered with testing; CG: no loss	Group-based Combination of education on the aging brain, computerized attention training, and in person mnemonic training with homework, stress management and "self-efficacy" were also addressed	8 weekly sessions of 120 minutes	Intervention end	Improved performance on face name association and word list delayed memory tasks for IG, no change in paragraph learning (study specific tasks)
Buschert et al. (2011) & (2012); Germany	RCT	2011: aMCI ^a (<i>n</i> = 10) 2012: f/u: (<i>n</i> = 10)	2011: active (<i>n</i> = 12) 2012: f/u (<i>n</i> = 10)	Recruitment: 27 screened, 3 chose not to participate prior to randomization, 24 recruited Attrition: 2 did not complete, 2 withdrew due to AD conversion, lack of interest prior to 15 and 28 month f/u	Group-based Cognitive training class with multiple techniques, including mnemonic training and "informal activities" to foster cognitive and social skills	20 sessions 2 hour sessions per week for 6 months	15 months 28 months	IG improved from baseline in global cognitive functioning to 28 months post intervention, immediate memory improved at 15 and 28 mo. f/u; different from CG in global cognitive functioning at 15 mo. f/u
Brum et al. (2009); Brazil	RCT	MCI ^a (<i>n</i> = 16)	MCI ^a (<i>n</i> = 18) Received intervention after final data collection	Not reported	Group-based Education and mnemonic training with time spent in session on orientation, face-name associations, visual/auditory attention exercises, mnemonics, and ADL practice	8 sessions, 2 hours per session, 2 sessions per week for one month	Intervention end	IG had significant improvement compared to CG for attention
Finn and McDonald (2015); Australia	RCT	aMCI ^b (single or multi) (<i>n</i> = 12)	aMCI ^b (<i>n</i> = 12) Minimal contact for measure completion	Recruitment: 31 recruited Attrition: 4 withdraw after randomization but before treatment due to medical/personal issues, 2 did not meet diagnosis criteria, 1 could not complete in 5 weeks	Individual-based Repetition lag training in learning words and discriminating them from incorrect "lures" that are then repeated at increasing lengths of time as the participant does well	Practice round plus six training sessions (long enough to complete 4 rounds of training), 5 weeks maximum	Intervention end	Improvement in memory for non-training word pairs in IG, but no effect on attention, concentration, or speed tasks

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Greenaway et al. (2013); USA	RCT	aMCI ^a single domain (<i>n</i> = 18)	aMCI ^a Calendar with no training (<i>n</i> = 17)	Recruitment: 61 contacted, 21 declined (most often due to driving distance to facility) Attrition: 2 withdrew prior to intervention, 1 withdrew before 8 week f/u, 2 withdrew prior to 6 month f/u	Individual-based Training of use of the Memory Support System calendar and note taking external aid	12 sessions, 1 hour each, for 6 weeks	8 weeks 6 months	No change in global cognitive functioning
Jean, Simard, et al. (2010); Canada	RCT	aMCI ^a (<i>n</i> = 11)	aMCI ^a Active time matched (<i>n</i> = 9); both groups had additional memory education	Recruitment: 22 total (no details given) Attrition: 2 lost in CG during training (overburdened with work = 1, travel = 1)	Individual-based Training of 10 faces with names Experimental = face name associations with errorless learning and spaced retrieval Control = trained with errorful learning	6 sessions, 45 minutes each, for 3 weeks	4 weeks	Both groups improved in ability to learn face-name associations (same list as trained)
Kinsella et al. (2009); Australia	RCT	aMCI ^{ab} (<i>n</i> = 22)	aMCI ^{ab} Waitlist (<i>n</i> = 24) at 2 week f/u 4 month f/u (<i>n</i> = 22)	Recruitment: 89 total referred (not interested (12), no time (9), could not contact (4), poor English 2; 8 used for pilot sample; 54 enrolled Attrition: 10 withdrew prior to 4 month f/u	Group-based Memory education and practice of mnemonic and external aid practices	5 sessions, 1.5 hour groups, once a week for 5 weeks	2 weeks 4 months	IG significantly improved prospective memory task of addressing an envelope at f/u
Konsztowicz et al. (2013); Canada	RCT	MCI (<i>n</i> = 8 memory training), (<i>n</i> = 7 memory compensation)	MCI 4 waitlist (re-randomized 2 each to interventions after 6 months)	Recruitment: 50 approached as eligible (8 could not be contacted, 18 not interested, 5 too busy, 1 death). Attrition: 3 withdrew (MT = 1 no longer interested, 1 couldn't hear sessions; MC = 1 disappointed with randomization)	Small group First session memory didactic; Memory training intervention = mnemonics; memory compensation = memory notebook	7 sessions, 90 minute, 1 session per week	Intervention end	Improved delayed word list recall in memory compensation group for unknown reason
Lam et al. (2015); Hong Kong	RCT	MCI ^b (<i>n</i> = 145)	MCI ^b Social (active) (<i>n</i> = 131)	Recruitment: 655 approached at senior centers, 100 not eligible, 555 enrolled Attrition: 132 did not complete	Group-based Cognitively-demanding activities (e.g. reading and discussing newspaper, board games, playing an instrument)	3 1-hour sessions per week, for 12 months	Intervention end	IG showed improvement over time on global cognitive scores, delayed memory, and verbal fluency
Nakatsuka et al. (2015); Japan	RCT	MCI ^d (<i>n</i> = 32)	MCI ^d Social (active) (<i>n</i> = 38)	Recruitment: 295 community-dwelling older adults approached; 127 agreed Attrition: 34 did not complete	Questions, puzzles, and games targeting attention and executive function	24 1-hour sessions for 12 weeks (12 weekly group sessions, 12 weekly at-home sessions)	Intervention end	IG improved in global cognitive function, processing speed and verbal fluency
Rapp et al. (2002); USA	RCT	MCI ^a (<i>n</i> = 9) After 6 months (<i>n</i> = 7)	MCI ^a (<i>n</i> = 10) By 6 months (<i>n</i> = 9)	Recruitment: 168 interested, 77 eligible for testing, 43 too impaired, 25 people	Group-based Education on memory/dementia,	6, 2 hour weekly group meetings	6 months	No significant change on cognitive testing.

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Rojas et al. (2013); Argentina	RCT	MCI ^a (<i>n</i> = 15) completed through 12 month f/u	MCI ^a Waitlist (<i>n</i> = 15)	approached, 19 agreed to participate Attrition: 3 withdrew before 6 month f/u Recruitment: 120 referred, 67 met MCI criteria, 21 not interested in study, 46 randomized Attrition: 9 left trained group, 7 left control group (4 converted to dementia, 8 "family reasons", 2 medical reasons/death, 2 not interested)	relaxation, workbook assignments, mnemonic strategies Group-based Cognitive Intervention Program vs. combination of cognitive stimulation (socializing), cognitive exercises, cognitive training in mnemonics, general information on MCI and external aids	2 hour sessions, 2 sessions per week for 6 months	6 months	Decline in CG in global cognition, memory recognition, and semantic fluency. Improvement in IG in naming and semantic fluency
Troyer et al. (2008); Canada	RCT	aMCI ^a (<i>n</i> = 23)	aMCI ^a Waitlist (<i>n</i> = 22)	Recruitment: 68 eligible, 5 declined, 9 used in pilot. 54 randomized Attrition: 3 withdrew before intervention, 3 did not complete, 3 withdrew before 3 month f/u	Group-based Combination of information, intervention training (both external and mnemonic) and homework practice	10 sessions 2 hour group sessions for 6 months	3 months	No impact on objective memory tasks of face- name learning, number learning, or wordlist learning
Vidovich et al. (2015); Australia	RCT	MCI ^e 10 weeks (<i>n</i> = 77) 1 year (<i>n</i> = 77) 2 year (<i>n</i> = 67)	MCI ^e Education 10 weeks (<i>n</i> = 79) 1 year (<i>n</i> = 77) 2 year (<i>n</i> = 60)	Recruitment: 324 assessed (114 ineligible; 50 refused), 160 randomized Attrition: 20 CG lost to f/u (13 declined, 3 died, 4 ill); 13 IG lost to f/u (10 declined, 1 died, 2 ill)	Group-based Cognitive activity training strategy with cognitive rehab, stimulation, and training elements versus education group control	10 sessions 90 minute sessions for 5 weeks	10 weeks 1 year 2 years	IG had significantly better digits forward compared to CG after 2 years, but actual amount of difference so small of uncertain significance

Note. MCI criteria used:

^aPetersen et al. 1999 or 2004;

^bWinblad et al. 2004;

^cAlbert et al. 2011;

^dMorris, 1993;

^ePortet et al. 2006.

aMCI = Mild cognitive impairment, amnesic subtype. CG = Control group. CT = Controlled trial. f/u = Follow-up. IG = Intervention group. MCI = Mild cognitive impairment. RCT = Randomized controlled trial.

Table 4

Everyday Outcomes of Therapist-based Intervention Studies

Reference	ADLs	Mood	QOL	Metacognition	Other
Belleville et al. (2006)			Wellbeing ^{*/+}	QAM Subtests Personal events/+ Places, Political, social events/+ Conversations/- Books and movies/- Slip of attention/- People/- Use of objects/- Actions of perform/-General/-	
Buschert et al. (2011) & (2012)		MADRS Intervention end/+ 15 months f/u/- 24 months f/u/- (<i>d</i> = 0.64, 10, 12)	QOL-AD Intervention end/- 15 months f/u/- 24 months f/u/- (<i>d</i> = 0.51, 10, 12)		6/12 in CG (who were given intervention after 8 months) converted to dementia. None in the first IG converted
Brum et al. (2009)	DAFS-R Subtests Orientation/+ (<i>d</i> = 0.93, 16, 18) Communication/- (<i>d</i> = 0.07, 16, 18) Finances/+ (<i>d</i> = 1.30, 16, 18) Shopping/- (<i>d</i> = 0.49, 16, 18) Total/+ (<i>d</i> = 1.30, 16, 18)	GDS/- (<i>d</i> = 0.53, 16, 18)			
Finn and McDonald (2015)		DASS-21 Subtests Depression/- (<i>d</i> = -0.24, 12, 12) Anxiety/- (<i>d</i> = -0.26, 12, 12) Stress/- (<i>d</i> = -0.32, 12, 12)		CFQ/- (<i>d</i> = 0.29, 12, 12)	
Greenaway et al. (2013)	E-Cog Intervention end/+ 8 weeks f/u/+ 6 mo f/u/- (<i>d</i> = 0.16, 18, 17)	CES-D 8 weeks f/u/- 6 months f/u/- (<i>d</i> = -0.04, 18, 17) REACH 8 weeks f/u/- 6 months f/u/- (<i>d</i> = 0.23, 18, 17)	QOL-AD 8 weeks f/u/- 6 months f/u/- (<i>d</i> = 0.03, 18, 17)	Self-Efficacy in MCI* 8 weeks f/u/- 6 months f/u/- (<i>d</i> = 0.26, 18, 17)	Care Partner CB 8 weeks f/u/- 6 months f/u/+ QOL AD 8 weeks f/u/- 6 months f/u/- CES-D 8 weeks f/u/- 6 months f/u/+ REACH 8 weeks f/u/- 6 months f/u/-

Reference	ADLs	Mood	QOL	Metacognition	Other
Jean, Simard, et al. (2010)	RBMT 1 weeks f/u / – 4 weeks f/u / – (<i>d</i> = 0.22, 11, 9) MMQ Ability 1 weeks f/u / – 4 weeks f/u / – (<i>d</i> = 0.27, 11, 9)	MMQ Contentment 1 weeks f/u / – 4 weeks f/u / – (<i>d</i> = –0.12, 11, 9)		MMQ Strategy 1 weeks f/u / – 4 weeks f/u / – (<i>d</i> = 0.62, 11, 9)	
Kinsella et al. (2009)	MMQ Ability subscale 2 weeks f/u / – 4 month f/u / – (<i>d</i> = –0.07, 22, 22)	MMQ contentment 2 weeks f/u / – 4 month f/u / + improved waitlist (opposite of hypothesized) (<i>d</i> = –0.13, 22, 22)		MMQ Strategy Use 2 weeks f/u / + 4 month f/u / + (<i>d</i> = 0.14, 22, 22) Strategy Knowledge* 2 weeks f/u / + 4 month f/u / + (<i>d</i> = 0.24, 15, 16)	
Konsztowicz et al. (2013)	MMQ Ability** Memory Trained/+ (<i>d</i> = 0.36, 8, 4) Memory Compensation/– (<i>d</i> = –0.04, 7, 4)	MMQ Contentment** Memory Trained/+ (<i>d</i> = 0.94, 8, 4) Memory Compensation/– (<i>d</i> = 0.30, 7, 4)		MMQ Strategy Use Memory Trained/– (<i>d</i> = 1.07, 8, 4) Memory Compensation/– (<i>d</i> = 0.54, 7, 4) MIC/+ (<i>d</i> = 0.09, 115, 101)	
Lam et al. (2015)	CDAD/– (<i>d</i> = 0.13, 115, 101) CDR/– (<i>d</i> = 0.15, 115, 101)	CSDD/+ (<i>d</i> = –0.05, 115, 101)			
Nakatsuka et al. (2015)		GDS-SF/– (<i>d</i> = –0.08, 32, 39)	Quality of Life Face scale* /– (<i>d</i> = –0.39, 32, 39)		
Rapp et al. (2002)	MCI Present Ability* Intervention end/+ 6 months f/u / + (<i>d</i> = 0.69, 7, 9) MFQ Frequency of Forgetting Intervention end/– 6 months f/u / – (<i>d</i> = –0.09, 7, 9) MFQ Retrospective Functioning Intervention end/– 6 months f/u / – (<i>d</i> = 0.31, 7, 9)			MFQ General Functioning Intervention end/– 6 months f/u / – (<i>d</i> = 0.26, 7, 9) MFQ Seriousness Intervention end/– 6 months f/u / – (<i>d</i> = 0.12, 7, 9) MFQ Mnemonic Use Intervention end/– 6 months f/u / + (<i>d</i> = 0.50, 7, 9) MCI Potential Improvement* Intervention end/+ 6 months f/u / – (<i>d</i> = 0.55, 7, 9) MCI Inevitable Decline* Intervention end/+ 6 months f/u / – (<i>d</i> = 0.15, 7, 9) MCI Effort Utility*	

Reference	ADLs	Mood	QOL	Metacognition	Other
Rojas et al. (2013)	CDR ^{**} /+ (<i>d</i> = 0.34, 15, 15) ADLS/-	NPI/-	QOLQ/-	Intervention end/- 6 months f/u/-	
Troyer et al. (2008)	MMQ Ability ^{**} Intervention end/- 3 months f/u/- (<i>d</i> = 0.81, 23, 22)	MMQ Contentment ^{**} Intervention end/- 3 months f/u/- (<i>d</i> = -0.03, 23, 22)		Memory strategy knowledge ^{*, **} Intervention end/+ 3 months f/u/+ (<i>d</i> = 0.31, 23, 22) Self-report strategy use during testing [*] Intervention end/+ 3 months f/u/- (<i>d</i> = 1.21, 23, 22) MMQ Strategy Use Intervention end/+ 3 months f/u/+ (<i>d</i> = 0.74, 23, 22)	
Vidovich et al. (2015)	SAILS ^{**} /- (<i>d</i> = -0.14, 66, 60)	PHQ-9 ^{**} /- (<i>d</i> = 0.05, 67, 60)	QOL-AD ^{**} /+ (<i>d</i> = 0.23, 67, 60)	MFQ Mnemonics Use ^{**} /+ IG reported significantly lower use of mnemonics in daily life (opposite of hypothesized) (<i>d</i> = -0.18, 67, 59) MFQ General Forgetting ^{**} /- (<i>d</i> = -0.12, 66, 58) MFQ Seriousness of Forgetting/- ^{**} /- MFQ Retrospective Functioning ^{**} /- (<i>d</i> = 0.45, 67, 59)	LAQ/- PAQ/- SNSQ/- 27/60 CG no longer MCI (reverted) at 2 years 25/67 IG no longer MCI 6 CG and 10 IG converted to dementia at 2 years

Note. Measures are provided with + or - to reflect whether it was reported as significantly different in the study. When it was possible to calculate effect size, those numbers are provided next to the relevant test (effect size, final number of participants treated by that time point, final number of comparison participants by that time point, positive effect sizes reflect greater improvement for treatment group relative to comparison group). Cohen's *d* effect size computed as [(posttest-treatment - pretest-treatment) / (posttest-control - pretest-control)] / (pooled baseline standard deviation of both groups). Outcomes without an effect size did not provide information necessary to compute standardized mean differences. CG = Control group. f/u = Follow-up. IG = Intervention group.

* Study-specific measure.

** Effect sizes computed as group differences in Cohen's *d* for published posttest-pretest changes.

Measures: ADLS (Activity of Daily Living Scale; Lawton and Brody 1969); CB (Caregiver Burden; Zarit 1990); CDAD (Chinese Disability Assessment for Dementia; Mok et al. 2005); CDR (Clinical Dementia Rating; Morris 1997); CES-D (Centers for Epidemiological Studies - Depression; Radloff 1977); CFQ (Cognitive Failures Questionnaire; Broadbent et al. 1982); CSD (Cornell Scale for Depression in Dementia; C. Lam et al. 2004); DAFS-R (Direct Assessment of Functional Status; Loewenstein and Bates 1989); DASS-21 (Depression Anxiety Stress Scale; Lovibond and Lovibond 1995); E-Cog (Everyday Cognition Memory Subtest; Farias et al. 2008); GDS-SF (Geriatric Depression Scale-Short form; Sheikh et al. 1986); LAQ (Leisure Activity Questionnaire; Verghese et al. 2003); MADRS (Montgomery-Asberg Depression Scale; Montgomery and Asberg 1979); MIC (Memory Inventory for Chinese; Cheong et al. 2006); MFQ (Memory Functioning Questionnaire; Gilewski et al. 1990); MMQ (Multifactorial Metamemory Questionnaire; Troyer and Rich 2002); NPI (Neuropsychiatric Inventory; Cummings et al. 1994); QAM (Questionnaire d'auto-évaluation de la mémoire; Van der Linden et al. 1989); PAQ (Physical Activity Questionnaire; Janrozik et al. 2000); PHQ-9 (Patient Health Questionnaire-Nine Item; Kroenke et al. 2001); QOL-AD (Quality of Life-Alzheimer's Disease; Logsdon et al. 2002); QOLQ (Quality of Life Questionnaire; Machnicki et al. 2009); RBMT (Rivermead Behavioral Memory Test; Wilson et al. 1989); REACH (Resources for Enhancing Alzheimer's Caregiver's Health; Wisniewski et al. 2003); SAILS (Structured Assessment of Independent Living Skills; Mahurin et al. 1991); SNSQ (Social Network Satisfaction Questionnaire; Koenig et al. 1993).

Table 5

Overview of Multimodal Intervention Studies

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Fiatarone Singh et al. (2014); Australia	RCT	MCI ^a Cognitive training and physical resistance training (<i>n</i> = 27)	MCI ^a Sham cognitive activity and exercise (<i>n</i> = 27)	Recruitment: 2,094 research participants approached, 1,994 not eligible (1,582 not interested, 214 on hold, 117 ineligible, 61 no contact, 17 withdrawn); 100 enrolled Attrition: 14 did not complete, 12 dropped out at f/u	Cognitive training: COGPACK [®] adaptive computerized exercises of memory, executive function, attention, and processing speed Physical resistance training: High intensity pneumatic resistance machines targeting most major muscle groups	100 minute session, 2–3 sessions per week, for 6 months	6 month (intervention end) 18 month (12 months post intervention)	Speed and attention mildly improved at f/u
Hwang et al. (2012); South Korea	RCT	aMCI ^a (<i>n</i> = 6)	aMCI ^a waitlist (<i>n</i> = 5)	Recruitment: Consecutive memory clinic outpatients (no details given) Attrition: 2 withdrew	Cognitive training: Individualized, multicomponent program (reality orientation, computerized attentional training, memory training, visuo-construction training, executive function training, abstract thinking, homework)	18 weekly sessions, 50-minutes each session	2 weeks 3 months	Verbal memory significantly improved at f/u, other cognitive domains trending towards improvement at follow-up
Joosten-Weyn Banningh et al. (2011); Netherlands	CT	MCI ^a (<i>n</i> = 47)	MCI ^a waitlist (<i>n</i> = 40)	Recruitment: 93 enrolled Attrition: 6 withdrew	Group-based therapy: cognitive behavioral therapy principles with psychoeducation and memory rehabilitation, coping skills	10 weekly sessions, 2 hours each session	6–8 months	
Joosten-Weyn Banningh et al. (2013); Netherlands	CT	Significant others of MCI patients (<i>n</i> = 58)	Significant other waitlist (<i>n</i> = 27)	Recruitment: 88 recruited Attrition: 3 withdrew after intake, 1 withdrew after intervention	See Joosten-Weyn Banningh et al. (2011)	See Joosten-Weyn Banningh et al. (2011)	Intervention end	
Kurz et al. (2009); Germany	CT	MCI ^b (<i>n</i> = 18)	MCI ^b waitlist (<i>n</i> = 12)	Recruitment: Consecutive enrollment from a university psychiatric day-clinic Attrition: No information	Structured group program involving practical problem solving, self-assertiveness training, stress management, relaxation training, journaling, creativity tasks, cognitive training (memory)	22 hours per week for 4 weeks	Intervention end	Verbal and nonverbal memory improvements

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Lam et al. (2015); Hong Kong	RCT	MCI ^b (<i>n</i> = 132)	MCI ^b Social (active) (<i>n</i> = 131)	Recruitment: 655 approached at senior centers, 100 not eligible, 555 enrolled Attrition: 132 did not complete	aids), and motor/ mobility exercises Cognitive-Physical training combined: One cognitive activity and two mind-body exercises	12-month intervention period Three 1-hour cognitive sessions per week Three 1-hour physical sessions per week	Intervention end	Improvement over time on global cognitive scores, delayed memory, and verbal fluency
Law et al. (2014); Australia	RCT	MCI ^c (<i>n</i> = 40)	MCI ^c Single blind, occupational therapy (<i>n</i> = 43)	Recruitment: 211 screened for eligibility, 128 excluded, 83 enrolled Attrition: 8 did not complete, 4 withdrew prior to 6-month f/u	Cognitive therapy: 30 minutes of computerized cognitive training (visual searching, forward-backward digit recall, and calculation), 30 minutes of cognitive strategy training. Sessions supplemented with homework	6 sessions for 10 weeks	6 months	Global cognition, executive function, and memory improvements at f/u
Reuter et al. (2012); Germany	RCT	Parkinson's Disease-MCI Cognitive training (<i>n</i> = 72) Cognitive training with transfer IG (<i>n</i> = 75) Cognitive training with transfer and motor training IG (<i>n</i> = 76)	Random assignment to one of the three IGs	Recruitment: Patients approached during an in- patient rehabilitation stay Attrition: 7 did not complete	Cognitive training: Planning, memory, decision making, concentration, problem solving, and summarization, relaxation and occupational training Cognitive training with transfer: Cognitive training plus application to everyday tasks of cognitive strategies and social skills (transfer). Additional relaxation and occupational training Cognitive training with transfer and motor training: All elements of cognitive training with transfer plus motor sequencing, dual- motor tasks, spatial orientation, walking, without additional	1 month intervention period Cognitive training: 4× week, 60 minute sessions, at least 14 sessions total Transfer session: 90 minute sessions, 3× week, at least 10 sessions total Motor training: 60 minute sessions, 3× week, 10–12 sessions total	1 month 6 months	All IGs improved in global cognitive functioning at f/u

Reference/Location	Type	IG	CG	Recruitment/Attrition	Intervention(s)	Sessions/Duration	Follow-up	Cognitive Outcomes
Schmitter-Edgecomb and Dyck (2014); USA	RCT	MCI ^{d/} Caregiver dyads (<i>n</i> = 23)	MCI ^{d/} Caregiver dyads (<i>n</i> = 23) Standard care: routine physician visits, monitoring of disease progression, active lifestyle maintenance, and in some cases AChE inhibitors and Namenda [®]	Recruitment: 98 dyads assessed for eligibility, 48 excluded, 55 enrolled Attrition: 2 dyads did not complete, 2 dyads withdrew after intervention completion but before post-testing	relaxation or occupational training Individualized orientation sessions, a half-day psychoeducation workshop, and "strategy training and problem solving" group sessions involving communication and social skills training, memory notebooks, skills training, and goal-planning skills	3-month intervention period "Strategy training and problem solving" sessions, 20 sessions total, 2 sessions per week for 10 weeks, 2 hours per session	Intervention end	Memory scores improved
Tsolaki et al. (2011); Greece	RCT	MCI ^a (<i>n</i> = 104)	MCI ^a Waitlist (<i>n</i> = 72)	Recruitment: 751 approached, 575 excluded (182 travel restrictions, 8 died, 12 medical problem, 321 dementia, 52 on AChEI), 176 enrolled Attrition: No information	Cognitive training (attention and executive function), cognitive stimulation (enhancement of episodic memory, semantic memory, autobiographical memory, mental imagery, and visual memory), and psychotherapeutic techniques (relaxation)	5-month intervention period 90 minutes per session, 3 sessions a day (1 of each component), 1 session per week, 60 sessions total (20 sessions of each component)	Intervention end	Global cognitive improvements

Note. MCI criteria used:

^aPetersen et al., 1999 or 2004;

^bWinblad et al., 2004;

^cAlbert et al., 2011;

^dMorris, 1993;

^ePortet et al., 2006.

AChEI = Acetylcholinesterase inhibitor. aMCI = Mild cognitive impairment, amnesic subtype. CG = Control group. CT = Controlled trial. IG = Intervention group. MCI = Mild cognitive impairment. RCT = Randomized controlled trial.

Intervention: COGPACK[®] (Marker 2008)

Table 6

Everyday Outcomes for Multimodal Intervention Studies

Reference	ADLs	Mood	QOL	Metacognition	Other
Fiatarone Singh et al. (2014)	BADL/-				
Hwang et al. (2012)			KQOL-AD 2 weeks f/u/- 3 months f/u/- (<i>d</i> = -0.60, 6, 5)	Self-Assessment of Cognition* 2 weeks f/u/+ 3 months f/u/-	
Joosten-Weyn Banningh et al. (2011)		GDS-15**/- (<i>d</i> = 0.20, 63, 30)	RAND-36-Dutch**/+ (<i>d</i> = 0.18, 63, 30) ICQ-Acceptance subscale**/- (<i>d</i> = 0.26, 63, 30) ICQ-Helplessness subscale**/+ (<i>d</i> = 0.20, 63, 30)	IQCODE/+	
Joosten-Weyn Banningh et al. (2013)					Caregiver Self-report: GDS-15/- ICQ-Acceptance subscale/- ICQ-Helplessness subscale/- IQCODE/- RAND-36-Dutch Wellbeing subscale/+ RMBPC hindrance/- RMBPC frequency/+ SCQ/-
Kurz et al. (2009)	BADL/+ (<i>d</i> = 0.38, 18, 12)	BDI-G/+ (<i>d</i> = 1.01, 18, 12)			
Lam et al. (2015)	CDAD/+ (<i>d</i> = -0.33, 93, 101) CDR/- (<i>d</i> = 0.00, 93, 101)	CSDD/+ (<i>d</i> = 0.05, 93, 101)		MIC/+ (<i>d</i> = 1.20, 93, 101)	
Law et al. (2014)	LIADL/- 6 months f/u/- (<i>d</i> = 0.73, 39, 32)				
Reuter et al. (2012)			PDQ-39 Cognitive training/- Cognitive training with transfer/- Cognitive training with transfer and motor training/+		
Schmitter-Edgecomb and Dyck (2014)	ADL-PI***/- (<i>d</i> = 0.23, 22, 19) EPPT Bill Paying/+ (<i>d</i> = 0.90, 21, 21) MMAA/+ (<i>d</i> = 0.56, 21, 22)	GDS-SF/- (<i>d</i> = 0.52, 18, 19)	QOL-AD/- (<i>d</i> = 0.04, 18, 19)	CSE/- (<i>d</i> = -0.26, 18, 19)	Caregiver Self-report: CSE/+ GDS-SF/- QOL-AD/-

Reference	ADLs	Mood	QOL	Metacognition	Other
Tsolaki et al. (2011)	FRSSD/+ ($d = 0.71, 104, 72$)				

Note. Measures are provided with + or – to reflect whether it was reported as significantly different in the study. When it was possible to calculate effect size, those numbers are provided next to the relevant test (effect size, final number of participants treated by that time point, final number of comparison participants by that time point, positive effect sizes reflect greater improvement for treatment group relative to comparison group). Cohen’s d effect size computed as [(posttesttreatment – pretesttreatment) – (posttestcontrol – pretestcontrol)]/(pooled baseline standard deviation of both groups). Outcomes without an effect size did not provide information necessary to compute standardized mean differences.

* Study-specific measure.

** Effect sizes computed as group differences in Cohen’s d for published posttest-pretest changes.

*** Reported by caregiver in reference to the patient.

Measures: ADCS-MCI-ADL (Alzheimer’s Disease Cooperative Study MCI Activities of Daily Living Scale; Galasko et al. 1997); ADL-PI (Activities of Daily Living-Prevention Instrument; Galasko et al. 2006); BADL (Bayer-Activities of Daily Living; Hindmarch et al. 1998); BDI-G (Beck Depression Inventory-German version; Hautzinger et al. 1994); CDAD (Chinese Disability Assessment for Dementia; Mok et al. 2005); CDR (Clinical Dementia Rating; Morris 1997); CSDD (Cornell Scale for Depression in Dementia; C. Lam et al. 2004); CSE (Coping Self-efficacy Scale; Chesney et al. 2006); EFPT (Executive Function Performance Test; Baum et al. 2007); FRSSD (Functional Rating Scale of Dementia; Hutton 1990); GDS (Geriatric Depression Scale; Yesavage et al. 1983); GDS-15 (Geriatric Depression Scale-15 item; Herrmann et al. 1996); GDS-SF (Geriatric Depression Scale-Short form; Sheikh et al. 1986); ICQ (Illness Cognition Questionnaire; Evers et al. 2001); IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly; De Jonghe et al. 1997); KQOL-AD (Korean Quality of Life-Alzheimer’s Disease; Shin 2006); LIADL (Lawton Instrumental Activities of Daily Living Scale Hong Kong; Tong and Man 2002); MIC (Memory Inventory for Chinese; Cheong et al. 2006); MMAA (Medication Management Ability Assessment; Patterson et al. 2002); PDQ-39 (Parkinson’s Disease Questionnaire; Jenkinson et al. 1995); RAND-36-Dutch (Van der Zee and Sanderman 1993); RMBPC (Revised Memory and Behavioral Problems Checklist-Dutch; Teunisse et al. 1997); SCQ (Sense of Competence Questionnaire; Vermooij-Dassen et al. 1996).

Table 7

Summary of Meta-analyses by Intervention Modality and Outcome Type

Group	k	d	95% CI	τ^2	p(Q)	Fail Safe N	Begg and Mazumdar's rank correlation (p-value)	Publication Bias Statistics			
								V&W 1	V&W 2	V&W 3	V&W 4
Intervention Modality											
Computer	15	0.31	0.12 – 0.51	0.00	.56	40	.00 (1.00)	0.24	0.13	0.28	0.23
Therapist	57	0.20	0.11 – 0.30	0.04	.43	618	.30 (< .001)	0.12	–0.82	0.17	0.14
Multimodal	19	0.31	0.08 – 0.54	0.19	.69	219	.12 (.48)	0.19	–0.96	0.27	0.23
Outcome Type											
Mood	26	0.16	0.03 – 0.28	0.02	.44	74	.26 (.07)	0.09	0.02	0.12	0.11
Metacognition	24	0.37	0.15 – 0.58	0.16	.88	301	.22 (.14)	0.23	–0.88	0.29	0.20
ADL	31	0.32	0.16 – 0.47	0.09	.65	366	.10 (.43)	0.21	–0.90	0.27	0.21
QOL	10	0.06	–0.11 – 0.22	0.00	.44	–9	–.11 (.66)	–0.00	–0.54	0.04	0.03

Note. k = number of outcomes included in this category; individual studies could contribute multiple outcomes; see Table 7 for classification of, and specific outcomes contributed by, each study; d = standardized mean difference in improvement for treatment minus comparison group. Positive values indicate greater improvement in the treatment group; 95% CI = estimated 95% confidence interval of the standardized mean difference; τ^2 = tau squared, a random effects estimate of the between-outcome heterogeneity in effect size, with larger values representing greater heterogeneity; p(Q) = probability associated with a random effects test of the null hypothesis of homogeneity, with non-significant values ($p > .05$) suggesting that we cannot reject the null hypothesis of homogeneous effect sizes among studies in this intervention modality; Rosenthal's (1979) Fail Safe N is the estimated number of studies that would need to exist to turn a significant population effect size estimate into a non-significant one; strong/significant Begg & Mazumdar's (1994) correlation coefficients are indicative of greater bias; V&W: Vevea and Woods (2005) adjusted effect size estimates under four conditions: 1 = Moderate one-tailed selection, 2 = Severe one-tailed selection, 3 = Moderate two-tailed selection, and 4 = Severe two-tailed selection. All publication bias statistics were estimated under random effects models.